Demography, Clinical Features, Etiology, Management and Outcomes in Acute Retinal Necrosis: A Prospective Study

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CERTIFICATE

This is to certify that this dissertation entitled "**Demography, Clinical Features, Etiology, Management and Outcomes in Acute Retinal Necrosis: A Prospective Study**" submitted to the Tamil Nadu Dr MGR Medical University, is a bonafide work done by **Dr Kamalakannan D**, under our guidance and supervision in the Department of Uvea, Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, Madurai during her residency programme from June 2015 –May 2018.

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DECLARATION

I, **Dr.Kamalakannan. D** hereby declare that this dissertation entitled, **"Demography, Clinical Features, Etiology, Management and Outcomes in Acute Retinal Necrosis: A Prospective Study"** is being submitted in partial fulfillment for the award of MS degree in Ophthalmology by The Tamilnadu Dr.MGR Medical University in the examination to be held in May 2018.

I declare that this dissertation is my original word and had not formed the basis for the award of any other degree or diploma award to me previously.

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PART I

INTRODUCTION

Acute retinal necrosis (ARN) is distinct ocular inflammatory condition, with constellation of clinical features and vision threatening complications. Acute retinal necrosis is visually devastating disease, prompt diagnosis and good therapeutic approach is a must for better visual recovery. Akira urayama et al [1]in the year 1971, reported six cases of a unique form of uveitis that had not been described before. They named this clinical entity as "kirisawa uveitis" after their professor Nagamori kirisawa. There report was the first documentation of ARN syndrome. The first international literature on acute retinal necrosis was by Willerson et al [2] in American journal of ophthalmology in the year 1977. The term bilateral acute retinal necrosis (BARN) was coined by Young and Bird[3] in the year 1978. Culbertson et al[4] in 1982 demonstrated presence of herpes virus in an enucleated eye of an ARN patient by electron microscopy, in the year 1986. Varicella zoster was cultured from ARN patient. In 1994 American uveitis society proposed a diagnostic criteria[5] for ARN syndrome. Despite, advances in treatment and diagnostic modalities available like polymerase chain reaction (PCR) to identify virus with intraocular fluid, ARN continues to remain as an ophthalmological emergency with retinal lesion progressing rapidly after the disease onset. Precise understanding about this disease condition by

ophthalmologist is at most important for prompt diagnosis and treatment to avoid vision loss.

EPIDEMIOLOGY

ARN was first reported in Japan, now reported throughout the world. ARN affect both gender, but has slight male preponderance. Acute retinal necrosis affects all age group, a bimodal distribution in age exist which peaks at 16-25 and 45-65 age groups. Bilateral involvement occurs in one third of patients, usually fellow eye involvement occurs between 1-6 weeks. A delay of several weeks to years had been reported in manifestation to occur in fellow eye.

ETIOLOGY

Many investigators believe ARN is a new disease, probably due to mutation of virus or due to host suitability, others believe that improved diagnostic methods and awareness of the disease led to increased state of being recognized. The main etiological factor for acute retinal necrosis is the herpes family virus of which alpha herpes virus Herpes simplex virus 1 (HSV1), Herpes simplex virus 2 (HSV2) and Varicella zoster (VZV) causes ARN most commonly. Rarely Epstein barr virus (EBV) and Cytomegalovirus (CMV) implicated to cause ARN. ARN may be a result of a dormant HSV1, HSV2 or VZV viral reactivation in retina. Since the causative viruses are neurotropic, the probable route for reaching the retina is to

travel down the optic nerve. Alternatively, one of other cranial nerves supplying the eye may transport the virus. The exact etiology of this reactivation still remain elusive, however an immuno genetic predisposition to the disease is likely. HSV1, HSV2 and VZV were found in ocular samples in high copy numbers suggesting active viral replication in patients with ARN. Evidence suggests that primary viral infection, in addition to a secondary reactivation, can cause ARN, I such cases virus can reach through haemtogenous route, with infected lymphocytes enabling the virus to cross blood retinal barrier.

IMMUNOLOGICAL ROLE

ARN was initially believed to be an acute immune disease. There had been studies about its immunological predispositions. Holland et al[6] demonstrated association of HLA-DQw7, phenotype DR4 and Bw62. An ARN patient generally shows no cell mediated and humoral immunity. In early phase of VZV ARN syndrome, a negative intra dermal varicella skin test which may indicate delayed hypersensitivity to VZV is frequently observed.

Increased serum antibody titer and lowering of delayed hypersensitivity response, is similar to condition in anterior chamber associated immune deviation (ACAID)[7].Experimental models, supports the role of herpes virus infection. Infection of herpes simplex virus type 1 in BAL B/C mice produces necrotizing vasculitis in the contra lateral eye within 10days. This animal model is similar to

ARN in humans. The disease developments in fellow eye only when the virus spreads through the optic nerve. As like other inflammatory eye disease, retinal damage, initially induced by infectious agent's leading to secondary immune response against previously sequestered retinal antigen. This secondary immune response can then propagate the inflammatory disease to the retina. ARN occurs suddenly without any warning in immunocompetent individuals. ARN is commonly seen in immunocompromised AIDS patients, ARN is seen in any stage of AIDS.

STANDARD DIAGNOSTIC CRITERIA FOR ACUTE REINAL NECROSIS[5]

The American uveitis society recommended diagnostic criteria to be used for all clinical and laboratory studies in acute retinal necrosis in the year 1994.

1. Focal, well demarcated areas of retinal necrosis located in the peripheral retina (outside the major temporal vascular arcade).
2. Rapid, circumferential progression of necrosis (if antiviral therapy has not administered)
3. Presence of evidence of occlusive vasculopathy
4. Prominent inflammatory reaction in vitreous and anterior chamber

Characteristics that supports but not required for diagnosis are

1.optic atrophy 2.scleritis 3.pain.

CLINICAL FEATURES[8]

1. SYMPTOMATOLOGY

At presentation, a patient with ARN typically complains of ocular or periocular pain mild to moderate grade. Irritation, foreign body sensation, usually associated with red eye. Pain is worse with ocular movement due to coexisting myositis and optic neuritis. In some patients pain, redness and photophobia is absent. Hazy vision, floaters and occasionally decreased peripheral vision seen in early course of the disease. Central vision loss is rare, seen as a result of centre involving retinal detachment and optic neuritis.

2. SIGNS

A. EXTERNAL AND ANTERIOR SEGMENT

During active disease mild to moderate conjunctival injection with cilliary flush is noted. Chemosis, lid edema, subconjunctival haemorrhage and even mild proptosis may been seen. Diffuse episcleritis , scleritis can develop. In AIDS patient concurrent viral keratitis or herpes zoster ophthalmicus seen occasionally. Mild to moderate anterior chamber reaction with fine or Granulomatous keratic precipitates are seen. Rarely hypopyon may occur. As anterior chamber reaction is not chronic and severe, formation of posterior synechiae is rare. Iris nodules like koeppes and busacca is unlikely. In ARN intraocular pressure (IOP) is frequently elevated. Alternatively, IOP may be reduced in ARN patients with chronic retinal

detachment(RD). iris neovascularisation may occur due to chronic retinal detachment. Cataract may occur mainly a posterior sub capsular cataract.

B.POSTERIOR SEGMENT

The triads of posterior segment findings are retinal and choroidal vasculitis, retinal necrosis and vitritis. Retinal vasculitis typically affect the arteries and is severe and oblitrative in nature. Narrowing of arteries and sheathing of large vessels especially within the area of necrosis. Retinal phlebitis is less prominent finding. Scattered, small to moderate sized hemorrhages noted corresponding to involved vessels.

Retinal necrosis appears ophthalmoscopically as confluent area of retinal whitening as small patches, broad zones of retinal necrosis are termed as "thumbprints" . The areas of active necrosis tend to be slightly thickened compared to normal retina and may have dull yellowish color. The border between necrotic and normal retina tends to appear quite well defined, smooth and geographic. There is preference for peripheral retina initially, with spread to macula occurring late, if at all, in the course of disease. Several noncontiguous patches of necrosis, each involving between one half to four clock hours of retina, in other instance the entire360 degrees peripheral retina is affected. As the disease progress the patches of retinal necrosis coalesce into broad geographic area. If the infection continues unabated, the leading edge of retinal necrosis advance to posterior pole at same

rate in all quadrants .The retinal necrosis usually develops at the same time or soon after retinal vasculitis. In some patients vasculitis component is more prominent than necrosis. It is theorized that the retinal necrosis in ARN occurs due to two separate mechanisms. 1. Direct cellular death from intracellular viral replication 2. Ischemic necrosis of the retina secondary to severe vascular occlusion.

An unusual pattern of necrosis that has relatively little inner retinal involvement initially, mild or nil vascular involvement, a rapid course, and relative sparing of areas adjacent to the retinal veins .This pattern represent a distinct form of ARN unique to immunosuppressed individuals. As retinal necrosis progresses large amount of vitreous cells and debris released in to the vitreous cavity. As a result visualization of posterior segment can be difficult at this stage. Severe vitreous fibrosis with traction resembling proliferative vitreoretinopathy is a common late complication.

Other posterior segment findings with ARN include optic disc swelling, branch arterial or venous obstruction can be seen at any point in the clinical course, secondary to severe vasculitis. Macular edema is reported to occur. ARN optic neuritis is heralded by optic disc edema, associated with decreased central vision. Along with presumed direct viral infection of the neural cells of the optic nerve as well as marked secondary ischemic necrosis due to widespread intra neural vasculitis, it is suggested that loculated exudates within the optic nerve sheath may

cause central vision loss in ARN. Typical optic neuritis due to ARN have swollen disc, acquired dyschromatopsia, a relative afferent papillary defect, central or arcuate field defect enlargement of optic nerve sheath.

VZV-ARN syndrome progress more rapidly than HSV-ARN. The granular peripheral lesion is the site of active viral proliferation. Progression of retinal lesion slows down on average 1 week after systemic antiviral therapy.

Retinal detachment corresponding to the site of necrosis occurs at a very high rate, ranging from 50% to 75% during the course of the disease. Necrotic retina is very thin with extremely weak adhesion and highly prone to tear in the area between the healthy posterior retina and necrotic peripheral retina.

C.ASSOCIATED SYSTEMIC FINDINGS

ARN has close temporal association with herpes zoster skin infections, herpes simplex ulcer. Concurrent aphthous ulcer reported in few patients. ARN may be accompanied with low grade fever, head ache, sinus pain and neck stiffness. CSF analysis revealed pleocylosis. Following ARN labyrinthine deafness and diffuse cerebral atropy had been reported. In light of this ARN is termed as " uveo-meningeal syndrome". Immunosuppressed patient present with concurrent viral encephalitis with ARN .

ACUTE RETINAL NECROSIS CLASSIFICATION[9]

Patients with ARN classified as

(I) *Presumptive ARN*: patients with features of ARN as described by American uveitis society diagnostic criteria

(II) *Probable ARN*: patients with features of ARN as per standard diagnostic criteria with history of systemic herpes infection.

(III) *Definite ARN*: patients with features of ARN as per standard diagnostic criteria with herpes virus DNA confirmation from aqueous or vitreous sample through PCR.

STAGES OF ACUTE RETINAL NECROSIS[10]

Stage I: necrotizing retinitis *(A)* discrete area of peripheral retinitis. *(B)* confluent peripheral retinitis, papillitis and macular edema

Stage II: vitreous opacification / organization

Stage III: regression of retinal necrosis. Secondary pigmentation of the lesion with contraction and condensation of vitreous base

Stage IV: Retinal detachment *(A)* acute retinal tears or detachment with traction or proliferative vitreoretinopathy. *(B)* chronic retinal detachment.

INVESTIGATIONS

A. LABORATORY INVESTIGATIONS

Complete blood count, liver function test, blood urea, serum creatinine, chest X ray, HIV titer, TPHA, FTA-ABS, acute and convalescent serum titer of HSV1, HSV2 and VZV.

RPR, FTA-ABS, ACE level, gallium scan, toxoplasmosis titer, CSF analysis are done in selected cases if diagnosis is doubtful with large cell lymphoma, CNS syphilis.

CT or MRI brain to look for optic nerve involvement and encephalitis.

ACE levels, Gallium scan to rule out sarcoidosis

B.POLYMERASE CHAIN REACTION (PCR)

PCR has proven to be a valuable test for diagnosis of ARN. The use of real time PCR allowed for the demonstration of high viral copy number in cases of ARN. PCR can be done with aqueous humour by anterior chamber paracentesis, vitreous sampling can be obtained by vitreous aspirate or by vitreous biopsy using vitreous cutter. There is still no adequate literature directly comparing anterior chamber paracentesis with vitreous tap to conclusively specify either method as clearly superior for PCR detection of virus in ARN. PCR analysis can also be used for monitoring disease course and assessing response to therapy. The viral load at initial presentation in ARN is correlated with the final visual outcomes. Higher

initial viral copy number was found to be predictive of patients ending with lower final visual acuity after a complete course of antiviral therapy. PCR analysis of ocular fluid can also be supplemented with calculation of a Goldmann-Witmer coefficient (GWC) in the diagnosis of ARN. GWC is a method of comparing intraocular antibody production to serum antibody production to diagnose ocular infection.

Although, data from PCR supports the role of herpes virus infection of ARN, it is difficult to recommend the use of PCR for diagnosis of ARN. First, vitreous sample is needed for analysis, which is an invasive procedure. Second, some caution in interpreting PCR data is warranted. PCR is so sensitive test that viral DNA from a previous infection years earlier may yield confusing results, especially because viral infection with herpes simplex, herpes zoster and CMV are quite common.

Nested PCR is highly sensitive, as small amount of targets are detected using 2 sets of primers. A double amplification process is used in this method. First set of primer is used for amplification, the product of this PCR is subjected to another PCR with second set of primer. The second primer used are specific to an internally amplified sequence to the first PCR, there by increasing the specificity of the test.

C.INTRAVENOUS FLUORESCEIN ANGIOGRAPHY

Intravenous fluorescein angiography in cases of ARN is not diagnostic but can be very useful in determining central vision loss, as well as documenting the extent of the infection. When the vitritis is severe, FFA is difficult to perform. Blockage of the underlying choroidal fluorescein pattern in areas of active retinitis is common. Area of active retinitis during venous phase little to no perfusion will be demonstrated, and both arteries and veins typically manifest an abrupt "cut-off" of intravascular fluorescein pattern. Such cut-off is highly suggestive of ARN, but may also be seen in other entities such as CMV retinitis, iatrogenic intravitreal aminoglycoside toxitity. Recirculation phase views may reveal staining of the optic disc, especially in cases with ARN optic neuritis. Staining of both arteries and vein secondary to the obliterative vasculitis is common, as is leakage from perifoveal capillaries, indicating the presence of macular edema. In the recovery phase of the infection, area of previously involved retina will demonstrate window defect from underlying retinal pigment epithelial alterations.

D.ULTRASONOGRAPHY

Ultrasonography (USG B scan) is very useful for detecting the presence of retinal detachment when the degree of vitritis hinders ophthalmoscopic examination of the posterior segment.

E. NEURO IMAGING

Computed tomography (CT) scan is done on patient with ARN will sometimes reveal optic nerve sheath enlargement. Magnetic resonance imaging (MRI) may show concurrent lesion of the optic nerve , tract, chiasma, and lateral geniculate body even in the absence of encephalitis. This suggests spread of infection via the axon of the ganglion cells.

F.FUNDUS PHOTOGRAPHY

Fundus photography is very important in documentation of ARN. Serial Fundus photography helps to assess treatment outcome.

G.INTRAOCULAR PRESSURE MEASUREMENT

Serial intra ocular pressure (IOP) measurement using applanation tonometer is mandatory. As ARN leads to both raised and lowered IOP according to clinical condition.

H.VISUAL ACUITY MEASUREMENT

Best corrected visual acuity (BCVA) must be recorded using standard test chart (Snellens) during initial presentation and in all follow up visits.

I.OPTICAL COHERANCE TOMOGRAPHY

Spectral domain (SD-OCT) or swept source (SS-OCT) helps to understand the functional consequence of ARN may be useful to monitor early sign of retinal detachment and to monitor macular involvement [11].

J.HISTOPATHOLOGY

Diffuse perivasular cellular infiltration involving all three ocular coats, with the retina and uveal tract most affected. The cellular infiltration mostly consists of lymphocytes and plasma cells with some acute inflammatory response in the form of polymorphonuclear leucocytes and occasional eosinophils. The predominant round cell infiltrate tends to center around arteries, with veins less frequently affected. The walls of involved vessels may be thickened and hyalinized. In area of active or severe necrosis, no recognizable retinal tissue persist, and only retinal vasculature remains intact. Eosinophilic intranuclear inclusion consistent with a herpes family virus may be seen. The enlargement infected retinal cells (cytomegaly) that is classic of CMV retinitis is rarely observed in cases of ARN. Transmission electron microscopy is useful for identifying cells harboring the causative virus in ARN.

TREATMENT

In the years following the initial break through linking herpes virus to ARN antiviral agents became the main stay of treatment along with adjutants like oral and topical corticosteroids, anticoagulants and topical cycloplegics.

1. ANTIVIRAL AGENTS

There is no consensus on optimal antiviral regime in the management of ARN. The standard of antiviral therapy is intravenous (iv) administration of acyclovir, newer oral antiviral agents are emerging as alternatives to high-dose intravenous acyclovir, avoiding the need for invasive and as an inpatient treatment. Combined oral and intravitreal antiviral therapy is gaining popularity; combined therapy improves visual and functional outcomes in ARN patients.

Drug resistant is uncommon and also be difficult to identify. Antiviral drugs have few side effects, but special attention needs to be paid to patient who have underlying renal disease, in pregnant and in immunocompromised patients.

The exact duration of treatment is still not conclusive. Clinical examination is the gold standard in monitoring treatment response and dose titration of antiviral. Newer methods, such as quantitative assays for viral DNA, may provide additional information and guide treatment in future.[12]

a. ACYCLOVIR

The antiviral effect of acyclovir was first described in 1977 and was the result of systematic search for a drug potential of exploiting the fact that viral infected cells are induced to produce thymidine kinase. The affinity for acyclovir for virus specific thymidine kinase is approximately 200 times greater than for cellular thyamidine kinase. There occurs rapid and preferential phosphorylation by

virus specific thymidine kinase to form acyclovir monophosphate, creating a concentration gradient. This favour uptake of infected cells in comparison to non infected cells. Host cell then complete the phosphorylation to acyclovir triphosphate, the active form of the drug. Acyclovir triphosphate inhibit viral replication by acting as a competitive inhibitor for viral DNA polymerase, which ultimately get incorporated in viral DNA chain and result in obligate chain termination. Replication of HSV is inhibited at concentration 3000 fold lower than those required to inhibit mammalian cell function. Acyclovir is highly specific for herpes infected cells; it is non toxic to uninfected cells.

Gastrointestinal absorption is slow, highly variable and incomplete. Oral bioavailability is 15% to 30%. Peak plasma concentration of acyclovir is 1.5times to 2.5 hours after oral administration and short plasma half life of 3 hours which necessitates frequent (5 times per day) dosing. The plasma concentration of 10-20microgram/ml can be achieved by intravenous (iv) administration of acyclovir of 5-10mg/ml, regular oral dose of 200-800mg yield 0.6-1.6microgram/ml. acyclovir is metabolized by liver and excreted by kidney. 15% of acyclovir is protein bound. Acyclovir is highly sensitive to herpes simplex virus. Intermediately sensitive to Varicella zoster and EBV, acyclovir is least sensitive to CMV.

Resistance to acyclovir is associated with mutation in the thymidine kinase gene as this is not required for viral replication. Viral stain resistant to acyclovir

are virtually always cross-resistance to other thymidine kinase dependent drug such as penciclovir and famciclovir. These stains are sensitive to foscarnet or cidofovir as these drugs inhibit viral DNA polymerase but they do not depend on thymidine kinase[12].

b. VALACYCLOVIR

Valacyclovir is the oral prodrug of acyclovir and has the same mode of action as acyclovir. Valacyclovir, the L-valyl ester of acyclovir, create a substrate for active transport in human intestine. After absorption valacyclovir under goes rapid and complete first pass metabolism in the intestine and liver to form acyclovir and essential aminoacid L-valine. This process is cytochrome P450 independent.

Increase uptake and rapid hydrolysis of valacyclovir to acyclovir results in significant greater systemic levels of acyclovir following oral valacyclovir ingestion compared with oral acyclovir. It had been found 3-5 fold increase in bioavailability of valacyclovir compared to oral acyclovir. Administration of valacyclovir 250mg 4 times daily results in acyclovir C_{max} and area under the concentration- time curve (AUC) values comparable to oral acyclovir 800mg 5times daily. Daily acyclovir AUC for valacyclovir at a dose of 1000mg 3 times are similar to those obtained with intravenous acyclovir 5mg/kg administration 3times/day. Valacyclovir 2000mg 4times daily produce a daily 109microgram /

hour /ml of AUC which is similar to AUC achieved by iv acyclovir 10mg/kg 3 times daily (107microgram/hour/ml)[12].

c. GANCICLOVIR

Gancyclovir is a synthetic nucleoside analogue of guanine which inhibits the precipitation of herpes virus both in-vivo and in-vitro. Intracellular gancyclovir is phosphorylated to gancyclovir triphosphate. Gancyclovir triphosphate is 100 times more concentrated in CMV infected cells than non infected cells. After, one hour iv injection of 5mg/kg gancyclovir sodium, total gancyclovir AUC 26.8microgram/kg/ml and C_{max} 9.0microgram/ml. intravitreal dose of gancyclovir 2000microgram in 0.1ml.Compared to acyclovir, gancyclovir has similar activity against HSV and VZV. The enhanced anti CMV activity is due to the lack of a hydroxyl group on the acyclic side chain.[13]

Early intravitreal injection with gancyclovir can yield satisfactory therapeutic effect and better visual acuity if applied before occurrence of retinal detachment.[14]

d. VALGANCICLOVIR

Valganciclovir is oral prodrug of gancyclovir and has same mode of action as gancyclovir. Evidence for use in ARN is scant. Savant et al[15] described a case of VZV ARN in an immunocompromised patient who was successfully treated

with valacyclovir. Bioavailability of Valganciclovir is increased 10 fold as compared to oral gancyclovir.[12]

e. FAMCICLOVIR

Famciclovir is the oral prodrug of peniclovir. Penciclovir is preferentially phosphorylated to penciclovir triphosphate, which act as a competitive substrate for DNA polymerase. The affinity of viral thymidine kinase penciclovir is 100 fold greater than for acyclovir but penciclovir triphosphate from is less effective than acyclovir triphosphate as an inhibiter of HSV DNA polymerase. The mean bioavailability of penicyclovir following a single dose of famciclovir is 77% and peak serum concentration are achieved within one hour.

f. FOSCARNET

Foscarnet selectively inhibits the pyrophosphate binding sites on viral DNA polymerase. Foscarnet, unlike acyclovir and gancyclovir, is not activated by thymidine kinase. Intravitreal application of foscarnet is preferred if no optic nerve and retinal toxicity is observed. Higher dose treatment at 2.4mg in 0.1ml has been found safe in treating retinitis.[16]

ADVERSE EFFECTS OF ANTIVIRAL DRUGS

Renal impairment is the most common side effect and is related to its renal excretion and poor water solubility. Rapid iv bolus administration increase the risk of acute renal failure, excess oral dosage also lead to renal failure. Renal function

usually recovers after drug cessation and volume resuscitation. Hemodialysis may be indicated in severe renal failure. Reduction of dose is essential in patients with renal insufficiency.

Acyclovir and valacyclovir belongs pregnancy drug category B, meaning there is no clear evidence of risk humans although there is no controlled studies available to document safety. Famciclovir is not recommended in pregnancy. Animal studies found gancyclovir to teratogenic, mutagenic and carcinogenic.

Table no.1: Summary of various antiviral drugs used in ARN[13]

	Acyclovir	***Valacyclovir***	***Famciclovir***	***Foscarnet***	***Gancyclovir***	***Valganciclovir***
DOSE	iv10-13mg/kg 3times per day for 5-10 days, then 400-800mg 5times daily for 6-8weeks per oral	1-2g 3times daily for 6-8 weeks	500mg 3times daily per oral for 12 weeks followed by taper for 13 weeks	2.4mg/0.1ml intravitreal as initial treatment	2000micogram in 0.1ml intravitreal as initial treatment	1g 3times daily per oral,900mg twice daily 3weeks induction, then 900mg daily for 2weeks before switching to oral acyclovir
USE	Current standard	Emerging standard	Acyclovir resistance	Systemic treatment contraindicated	As substitute to existing regime, in combination therapy	As a substitute to existing regime
ADVERSE EFFECTS	CNS toxicity, lethargy,delirium,seizures,renal failure	Hemolytic uremic syndrome, thrombocytic purpura	Contraindicated in pregnancy	Nil reported when given intravitreal	teratogenic, mutagenic and carcinogenic	Myelotoxicity, sterility, CNS abnormalities

2.CORTICOSTEROIDS

Various combination of systemic, periocular and topical corticosteroids have been employed to treat the inflammatory reaction in ARN. Systemic corticosteroid therapy appears to suppress the intraocular inflammation, and clear the vitreous reaction. Systemic corticosteroids have no effect on arresting retinal necrosis. There is a theoretical contraindication for concurrent administration of systemic corticosteroids with antiviral drug, as systemic corticosteroids would cause immunoinhibitory effect. The usual dose of oral corticosteroid (Prednisolone 1mg/kg/day) for one week, followed by tapering dose over 2-6 weeks(10mg per week).

Concomitant use of topical corticosteroids to treat anterior segment inflammation is advocated.

3.ANTITHROMBOTIC THERAPY

Antithrombotic therapy is given to prevent vascular obstructive complication of ARN. Aspirin and systemic corticosteroids in combination were found to normalize this hyper coagulation state. Some investigators recommend systemic anticoagulants like warfarin or heparin. This unproven therapy runs high risk of systemic morbidity and mortality.

Oral anticoagulant Aspirin 125mg-300mg one a day remain a reasonable choice in ARN.

4.CYCLOPLEGICS

In case of severe anterior segment inflammatory reaction, topical cycloplegic (2% homatropine 2times/day or 1% atropine 2 times/day) can be given in early stage of disease.

SURGICAL MANAGEMENT

Retinal detachment is frequent complication in ARN. The rate of retinal detachment may be as high as 85% even after treatment with antivirals. Measures for prevention or treatment of retinal detachment in ARN include

1. Prophylactic photocoagulation
2. Pars plana vitrectomy, endolaser photocoagulation and long acting tamponade and antiviral lavarge.
3. Optic nerve sheath fenestration

1. PROPHYLACTIC PHOTOCOAGULATION

It had been reported that prophylactic photocoagulation without vitreous surgery is effective for preventing retinal detachment.[17] Prophylactic laser treatment was applied on normal retina to surround the posterior edge of the necrotic retina by 3 consecutive rows of confluent and circumferential laser burns for extensive necrosis or diffuse patchy necrosis or up to the ora serrata for sectoral necrosis. Patches of necrosis were surrounded. Prophylactic laser treatment could not be applied if there is severe media opacity due to vitritis.

2. VITREOUS SURGERY

Prophylactic vitreous surgery is mostly indicated in patients who respond poorly to medical treatment and retinal lesion progress to involve the posterior pole. Vitreous surgery is recognized as a procedure in case of rhegmentogenous retinal detachment, one of the main late stage complications in ARN.

The merits of prophylactic vitreous surgery

1. Removal of vitreous opacities, enabling precise assessment of the retinal lesion, as well as improvement in visual acuity
2. Cutting the vitreous strands release the retinal tissue from traction, along with silicon oil implantation prevents retinal detachment.
3. Removal of vitreous eliminate the inflammatory cells and cytokines in vitreous cavity. Irrigation with antiviral drugs help the drug to directly act on the necrotic lesion.
4. Vitreous obtained from surgery used to confirm viral diagnosis.
5. Endolaser is applied to demarcate the necrotic areas.

Some patients undergoing vitreous surgery had retinal breaks during the procedure. In patients with retinal detachment gas tamponade is not believed to be adequate. Silicon oil tamponade is ideal for aiding retinal detachment. Silicon oil remaining in eye for long term would lead to secondary glaucoma and band shaped

keratopathy. The judgment of proper timing for silicon oil removal is one of the challenging decision in ARN treatment.

3.OPTIC NERVE SHEATH FENESTRATION

The entity of ARN optic neuritis produce acute central vision loss. It manifest as optic disc edema, optic nerve dysfunction such as acquired dyschromatopsia and enlargement of optic nerve sheath. Sergott introduced optic nerve fenestration in this condition. This unconventional treatment modality requires confirmation.

COMPLICATION AND SEQUELAE

The ocular inflammation associated with the ARN syndrome is generally a self limiting process. Without treatment, the active posterior segment inflammation eventually subsides. The host immune response controls the infecting virus. One feature of ARN syndrome that sets it apart from other infectious and inflammatory retinal condition is frequent development of *full thickness retinal hole.* These holes appear during the recovery phase of the infection. They are typically large, multiple, posterior in location and irregular in shape. Both full thickness retinal necrosis and secondary vitreous fibrosis with traction are responsible for the development of the retinal defects. Most observers note that retinal holes in ARN develop at the junction of normal and affected retina. Retinal tears accompanied by vitreous fibrosis and traction lead to *rhegmentogenous retinal detachment* and proliferative vitreoretinopathy in 75% of ARN patients.

Retinal detachment accounts for the bulk of ocular morbidity associated with the ARN syndrome. As retinal tears do not form during active inflammation, retinal detachment occurs between 6-12 weeks following the onset of symptoms but it had reported as early as one week following onset of symptoms. *Exudative retinal detachment* can develop in early stage of disease in conjunction with the active inflammation.

An unusual sequence of ARN syndrome is development of *retinal and optic neovascularization with vitreous hemorrhage* which occurs due to combination factors including chronic retinal detachment, inflammation induced angiogenic activity, severe retinal capillary nonperfusion from vascular occlusion.

If patient suffered retinal detachment and it progressed to chronic form and would end up in *phthisis bulbi.*

The entity of *ARN optic neuritis* produce acute central vision loss. It manifest as optic disc edema, optic nerve dysfunction such as acquired dyschromatopsia and enlargement of optic nerve sheath

Secondary glaucoma is frequently observed as a sequelae of ARN. *Cataract* mostly of posterior subcapsular variant is frequently observed.

Multiple occurrence of ARN separated over long period of time can rarely happen in the same eye.

DIFFERENTIAL DIAGNOSIS

Any disease process that produces retinal whitening with vitreous cells should be considered in differential diagnosis of ARN syndrome.

Progressive outer retinal necrosis syndrome (PORN) : retinal lesion in PORN involves predominantly deep retina, where as lesion in ARN is full thickness. Posterior retinal lesion is common in PORN. Anterior chamber reaction is common in ARN. PORN progress more rapidly and no vascular inflammation is found. It is most often seen in immunocompromised patients unlike ARN found in immunocompetent patient.[18]

CMV retinitis occurs almost exclusively in immunocompromised patients. Clinical course is more protracted than ARN. CMV retinitis is believed to be hematological spread. CMV induced retinitis is more apt to be posterior located early in disease course. Retinal detachment occur in ARN, but not frequent as in ARN.

Toxoplasmosis causes focal retinitis with vitritis. In immunocompromised host, diffuse toxoplasmosis results in widespread necrosis with severe vitritis can be quite difficult to differentiate from ARN.

Ocular syphilis can produce retinal arteritis, patchy retinal opacification and vitreous inflammation resembling ARN

Acute multifocal hemorrhagic retinal vasculitis shares certain similarities with ARN syndrome, with anterior segment inflammation signs, white retinal infiltrates, and retinal vasculitis. Higher incidence of and lower incidence of retinal detachment.

Large cell lymphoma closely resemble ARN, it has chronic course and acute inflammatory signs not typically seen. Large cell lymphoma produce subretinal involvement with retinal pigment epithelial detachments.

Behcets disease shares many similarities with ARN. Diffuse uveitis, a prominent retinal vasculitis, patches of retinal whitening. The retinal whitening in behcets disease in contrast to ARN involves only smaller area with no propensity to periphery. Anterior segment finding is more in behcets disease.

Sarcoidosis is a systemic disease whose ocular finding mimic ARN. Uveitis, vasculitis are common to both. But retinal whitening is not seen in sarcoidosis. *Endogenous or exogenous bacterial and fungal endophthalmitis* produce signs and symptoms similar to ARN. History of recent trauma and surgery and evidence of systemic nidus of infection would differentiate from ARN.

Retinoblastoma in childhood may be confused with ARN. In retinoblastoma no anterior segment inflammation is seen, intraocular calcification is seen. Acute ophthalmic artery obstruction or ocular ischemic syndrome can produce retinal

whitening in posterior pole. Vitritis is absent. *Commotion retinae (Berlins edema)* cause diffuse retinal whitening, antecedent history of blunt trauma present.

PROGNOSIS

It is worth repeating that visual prognosis in ARN depends mainly on the duration from onset to treatment. Most of the patients end up in poor vision in spite of treatment. Reports indicating that quantifying viral copy number in ocular fluid could be used to decide the treatment course as well as to predict the visual prognosis. ARN is a disease that undermines the retinal tissue at every moment after onset, and for this reason it is an emergent ocular disease that threatens the vision. In order to diagnosis and treat at the earliest stage possible, it is essential for ophthalmologist to assess the ocular finding in precision.

REVIEW OF LITERATURE

Review of literature was done with PubMed search. Keywords used were Acute retinal necrosis and ARN.

Urayama et al[1] in the year 1971 in Japan, reported about treatment of 6 patients who presented with acute onset of panuveitis and retinal arteritis. None of the patient is immunocompromised. Widespread retinal necrosis seen, and eventually all 6 patients developed retinal detachment. They reported these cases in Japanese literature as "kirisawa uveitis"

Willerson et al[2] reported about 2 patients with bilateral necrotizing vaso occlusive retinitis. Both patient developed retinal detachment. This was the first English literature about ARN. It was published in the year 1977.

Young and bird[3] in the 1978 named this disease entity as Acute Retinal Necrosis (ARN)

Hui-Ping Chen et al[19] reported about ARN in 9 patients 11 eyes, they found bilateral involvement in 2 of 9 patients(22%). All PCR for herpes simplex virus was negative. 6patients progressed to RD. the percentage of eyes with ambulatory visual acuity was 36.3%. Visual acuity was preserved in 27.3% at last visit.

T F Cochrane et al [20] through a prospective study carried out by carried out by British Ophthalmological Surveillance Unit (BOUS) between September 2007 to October 2008. Questionnaires was sent to ophthalmologist who reported ARN. 45

confirmed case with 52 eyes reported. Minimum incidence of 0.63 cases per million population per year was reported in United kingdom. Age ranged from 10years to 94 years. Males 55.6%, females 44.4%. bilateral involvement occurred in 15.6%. 2 cases had fellow eye involvement 3 weeks after first eye. 28% were immunocompromised. 30.7% developed RD occurred between 4-11 weeks. Varicella zoster followed by herpes simplex found to be most common causative agents. 24% patients received only oral antiviral, 47% patient received intravitreal antiviral. Visual outcome at 6months was less than 6/60 in 48% of affected eyes.

C.Iwahashi-Shima et al[21] 104 patients with ARN was studied. Retinal involvement at presentation was divided into 4 group. Zone1 involving posterior pole (n=22), zone 2 involving mid periphery (n=54), zone 3 involving periphery (n=25) and unknown (n=3).HSV was found in 18 eyes, VZV in 84 eyes and unknown in 2eyes. 48 patients underwent prophylactic vitrectomy, 28 patient out of 48 patient had their retina attached (58.3%). At one year 56 eyes (53.8%) had BCVA 20/200 or worse.

Joanna Brydak - Godowska et al[22] studied 10 patients aged between 19-55 years of age, all were diagnosed and treated for self limiting ARN. All patients was given acyclovir 800mg 5times per day, prednisolone 40-60mg per day, aspirin was given. In 6 patients treatment continued for 6months and discontinued after

resolution of inflammation. 4 patients had chronic inflammation. Encephalitis and meningitis occur in 2patient during course of treatment.

M N Muthiah et al[23] 12 month active case ascertainment study was carried out between march 2001-march 2002. Records of cases of ARN presenting to ophthalmologist via British Ophthalmological Surveillance Unit (BOUS) reporting system. 74 cases of ARN from 58 consultants reported. 31 patients was included in the study. 7 patients was immunocompromised. 22 were males, 9 females. Age ranged from 13-85years. 3 patients had bilateral involvement. Sudden vision loss was reported in 85.5%, photophobia 54.5%, ocular pain 25.8%, flu like symptoms 26.1%, red eye 16.1%, anterior chamber inflammation 80.6% and vitritis 83.9%. RD occurred in 12 patients (38.7%). Time of RD occurrence was 1-6months. VZV was commonest 56%. 21 patients had oral antiviral alone. It was found the incidence of ARN in UK population to be 1case per 1.6 to 2 million population per year.

Jost Hillenkamp et al [24] a cohort of 27 HIV negative ARN patients was studied through non randomizes, retrospective, interventional, comparative, consecutive series study was done. 3 patients had bilateral ARN. Vitreous biopsy was done for viral diagnosis. Group A: patients treated with acyclovir with oral prednisolone (n=22 eyes), Group B: patients treated with early vitrectomy, intravitreal acyclovir lavarge, laser demarcation of necrotic area when feasible, with or without sclera

buckling, gas or silicon oil tamponade (n=10 eyes). VZV found in 26 eyes, HSV in 5eyes and EBV in 2eyes found in conjunction with VZV. In Group A 18 out of 20eyes had RD, in Group B 4 out of 10eyes had RD p=0.007. Phthisis bulbi in Group A 2 out of 20eyes, no phthisis reported in Group B. mean BCVA at presentation was 1.09, mean final BCVA was 1.46, without significant difference between two Groups.

Chun H Lau et al [17] A cohort of 22 HIV negative patients with ARN studied through non randomizes, retrospective interventional, non comparative series study. 17 patients had unilateral ARN, 5 patients had bilateral ARN. Diagnostic vitrectomy for PCR viral DNA analysis done. Prophylactic barrier argon laser done posterior to necrotic retina to prevent RRD was done. Intravenous acyclovir with oral antiviral and vitrectomy for RD repair was done. VZV 66.7%, HSV 22.2% and EBV 16.7% seen in conjunction with VZV, PCR was negative in 11.1% of eyes. Systemic corticosteroid did not help to prevent RD (p=0.69). RRD occurred in 35.3% of eyes given prophylactic argon laser treatment and 80% of non laser eyes. 96.3% of RRD occurred between 3weeks to 5months. Visual acuity in patients underwent surgical treatment for RRD improved relatively.

Maurizio La Cava et al[25] A retrospective, interventional case is described in a 64 year old man complained of blurred vision in left eye. Patient had history of presumed ARN in right eye at 18 years of age. The reduced visual acuity and

ocular findings lead to diagnosis of delayed onset bilateral ARN. This report the longest reported interval of ARN quiescence with essential bilateral involvement and illustrates the importance of long term follow up in immunocompetent patients.

Leon D Charkoudian et al[26]Reported 2 cases of ARN following varicella vaccination. While post immunization infection is rare, clinician should be aware of this potential complication of the vaccine.

Ruwan A. Silva[27]A retrospective, observational, case series study of 14 patients 15 eyes all aged 21year or younger with ARN. Patient was diagnosed by various techniques including PCR of aqueous, vitreous, serum and antibodies in serum. Mean age was 11.7 with standard deviation of 7.0 years. Mean initial vision was 20/200, mean final vision was 20/400. In all patients HSV 2 was found. One patient has HSV 2 intrauterine infection. It was concluded that HSV 2 should be considered the primary candidate virus in pediatric population.

Beeran Meghpara[28]32 patients was diagnosed with ARN. 25 patients had at least 1 follow up visit. Intravitreal gancyclovir/ foscarnet was administered in 11 of 25 patients. Intravenous and oral antiviral was given in 14 and 19 patient respectively. 5 of 25 patients had retinal detachment. None of 6 eye treated with prophylactic laser detached. They concluded that greater extent of retinitis resulted in worse

visual prognosis. Patients with moderate disease did well with intravitreal therapy. In prophylactic laser patient had decreased occurrence of RD.

Roger Wong[16] The purpose of the study was to find the effect of intravitreal foscarnet and the clinical difference between VZV and HSV induced ARN. It was a retrospective comparative case series of 74 patients and 82 eyes. 32 eyes had HSV ARN, 48 patients VZV ARN. Average age of HSV ARN 34years and VZV ARN 51($p< 0.001$). visual acuity was similar on presentation after 12 month follow up, greater degree of visual loss in VZV ARN (0.4 LogMAR) compared to HSV ARN (0.04 LogMAR) ($p=0.016$). Retinal detachment was 2.5 times more common in VZV ARN than HSV ARN. When comparing eye treated with and without intravitreal foscarnet, there was 40% occurrence rate of RD. They concluded that viral identification had a key role in treating the patients. Intravitreal foscarnet is a good adjuvant in treatment of ARN to reduce the rate of RD.

Christina J. Flaxel et al[9]The purpose of the study is to compare the outcome of combination systemic and intravitreal therapy with systemic antiviral alone in treatment of ARN. A retrospective, interventional, comparative study of 29 eyes in 24 patients with ARN treated form 1987 to 2009. Mean age 42.6 years, mean follow up 44 months. 12 patients (14 eyes) treated with combined therapy and 12 patients (15eyes) treated with systemic antiviral only. PCR done in 14 patients,

positive in 11 patients. VZV= 2 PATIENTS (18%), HSV 1= 5 (45%) and HSV 2= 3 patients (27%). Kaplan meyer survival analysis revealed patients receiving combined therapy were more likely to have visual acuity 2 lines or better (p=0.006). Of the 29 eyes 13 eyes (45%) developed RD (4 eyes in combined group and 9 eyes in systemic group). Of the 13 eyes 12 patients underwent surgical repair procedure. 7 patients had macula off preoperatively. 6 patients underwent PPV, Endo laser, silicon oil . 1 patient underwent sclera buckle with cryotherapy. 5 patients underwent PPV, SB, EL, SO. 4 eyes retina remained attached after silicon oil removal.

Emerson et al[29]The purpose of the study is to explore the possibilities of oral antiviral therapy in lieu of intravenous acyclovir for treating ARN. It is a retrospective, interventional, small case series. 4 patients 6 eyes was studied. Patient was treated with valacyclovir 1g 3 times per day or oral famiciclovir 500mg 3times per day,topical and oral corticosteroids. Duration of antiviral ranged from 5 weeks to 3 months. Visual acuity increased in 3 patients, 1patient developed RD. They concluded oral antiviral alone is effective for indolent cases of ARN.

Taylor et al[30]The purpose of the study was to find the outcome of oral valacyclovir as a sole antiviral therapy in patients with ARN. Retrospective, interventional, case series study of 10 eyes. 8 patients received oral valacyclovir 2g

tds, 1 patients received 1g tds. A final BCVA 20/40 or better in 60% of eyes. 3 of 10 eyes (30%) developed RD. The final BCVA in patients treated with oral valacyclovir is comparative to intravenous acyclovir.

Calvo et al[31]The purpose of the study is to compare the visual acuity outcome and clinical feature with quantitative PCR DNA copy number in patients with ARN. 14 eyes of 13 patients was studied. PCR of aqueous fluid analyzed in 11 of 14 patients. VZV=7 eye (50%), HSV= 4 eyes (28.5%). Mean DNA copy was 7.9x 10^6/ml. quantitative DNA copy number > 5.0x10^6/ml is associated with extensive retinitis, worse visual acuity, development of RD in patients with ARN.

Chiun-Ho Hou et al[32]4 eyes in 4 patients from 199 to 2001 was operated for RD associated with ARN. Surgical method include pars plana vitrectomy (PPV), lensectomy, encircling sclera buckling combined with membrane dissection, air-fluid exchange, endolaser, retinal tamponade and silicon oil (SO) or per fluro propane gas. 3 patients needed one operation, one patient needed second surgery. Macular attachment achieved in all 4 eyes (100%). Visual acuity in 2 patients better than 20/200. Complication like cataract seen in 3 patients, macular pucker in 3 patients and silicon oil keratopathy in 1 patient.

McDonald et al[33]9 eyes in 8 patients with RD associated with ARN was operated. Patient was treated with sclera buckle, vitreous surgery or combination of treatment. Vitrectomised eye underwent combination of lensectomy, membrane

dissection, sclera buckle, air-fluid exchange, endolaser, retinal tamponade with C_3F_3 or SF_6 gas. Macular attachment attained in 8 eyes (89%). Vision improved in 78% eyes. Poor vision outcome observed in viral infected optic nerve, macular involvement, macular hole formation, macular pucker or hypotony.

Yong-Heng Luo et al[34]The purpose of the study was to compare the efficacy of prophylactic vitrectomy for ARN with routine treatment. 37 eyes were retrospectively studied. Patients were divided in 2 groups. One group was given routine treatment with antiviral medications and vitrectomy after RD (n=21) . In another group, prophylactic vitrectomy with antiviral medication was given (n=16). In routine treatment group 15 eyes progressed to RD, in prophylactic vitrectomy group 2 eyes progressed to RD (13%). They concluded that prophylactic vitrectomy can prevent RD and improve the progression of ARN.

Ishida et al[35] the purpose of the study is to evaluate the efficacy of prophylactic vitrectomy for ARN. 17 patients 18 eyes was studied. Retinal necrosis at initial presentation was classified according to Holland classification. All zone 1 eyes developed despite PPV, 8 of 12 zone2 eyes treated with vitrectomy developed RD. 3 of 4 zone2 eyes without PPV developed RD. all zone3 eyes cured with antiviral medication. They concluded that PPV is essential in prevention of RD in eyes with zone2 retinal necrosis.

Tibbetts et al[36] a cohort of 58 patients, diagnosed with ARN between 1981-2008. Cohort was subdivided into patients receiving acyclovir alone (n=36) and patients receiving newer antivirals (n=22). Outcomes was similar in both groups, visual acuity was 20/200 or worse in both group (p=059).

Takase et al [37] the purpose of the study is to develop and validate new diagnostic criteria for ARN based on ocular findings, clinical course and virological testing of intraocular fluids. Clinical features included 6 early stage ocular findings [1a] anterior chamber cells or mutton fat keratic precipitates. [1b] yellow white lesion [1c] retinal arteritis [1d] hyperemia of the optic disc [1e] inflammatory vitreous opacities [1f] elevated IOP. 5 clinical courses [2a] rapid retinal lesion expansion circumferentially [2b] development of retinal breaks or retinal detachments [2c] retinal vascular occlusion [2d] optic atrophy [2e] response to antiviral agents. PCR or Goldmann-Witmer coefficient for HSV or VZV was tested. Analysis of data delineated 2 level of diagnosis "virus confirmed ARN" and "virus unconfirmed ARN". The new diagnostic criteria was applied to 45 patients with ARN and in 409 patients with control uveitis sensitivity was 0.89, specificity = 1.00, positive predictive value = 1.00 and negative predictive value = 0.99. They concluded that newer diagnostic criteria of ARN was found to achieve high statistical value.

STUDIES OF ARN FROM INDIA

Roy et al[38] the purpose of the study was to determine the viral diagnosis and clinical outcome of eyes with ARN. A retrospective analysis of 62 eyes of 53 patients between 1997 to 2007 with features of ARN. Aqueous and vitreous sample revealed HSV in19 (30.6%) and VZV in 28 patients (45.16%). 41 eyes (66.12%) eye had RD. prophylactic laser was done in 19 eyes, surgical intervention was required in 32(51.6%) eyes. Favorable functional outcome was seen in 18 patients (45.1%).

Grover et al[39] 5 patients of ARN was investigated foe HSV and VZV. 3 patients with VZV IgM positive, 2 patient was positive with blood sample, one from vitreous sample. They concluded that VZV is a main causative agent for ARN in north India.

PART II

PART II

AIM

To Describe the Demographic Profile, Clinical Features, Etiology, Treatment modalities, Visual Outcome and Complications in Acute Retinal Necrosis.

OBJECTIVES

1. Find rate of occurrence of retinal detachment
2. To study the treatment outcome and long term complication in Acute retinal necrosis patients treated with oral and combined antiviral therapy.
3. Incidence Fellow eye involvement following primary ARN in unilateral ARN at presentation

MATERIALS and METHODS

STUDY TYPE

Prospective, observation, hospital based case series study

INCLUSION CRITERIA

All patients diagnosed to have acute retinal necrosis and had clinical features as described in standard diagnostic criteria by American Uveitis Society 1994[5] and given informed consent to take part in the study.

EXCLUSION CRITERIA

Patients diagnosed to have ARN, but not willing to take part in study.

METHODOLOGY

Source of data

All patients who attended uvea clinic, in a tertiary eye care hospital in south India.

Period of study

The study period was from 1st December 2015 to 30th May 2017. Patient was recruited for a period of one year (1st December 2015 to 31st December 2016) and subsequently each case was followed up for 6 months duration.

Method

Patient recruitment started after institute review board (Ethical committee) approval of the study. Informed consent was obtained from all participants of the study.

HISTORY: A detailed history was obtained from the patient regarding is ocular complains mainly his symptoms at presentation and history regarding any viral infection suffered by the patient and if present the type of viral infection was documented. Associated systemic illness was documented, in particular AIDS, as patients with AIDS are grouped as immunocompromised otherwise patients are grouped as immunocompetent.

Data sheet was prepared to record the demographic data of the patient like 1.Age, 2.Gender and 3.laterality of eye involved.

OCULAR EXAMINATION: A complete ocular examination was performed which included

- Best corrected visual acuity by using Snellen's chart
- Slit lamp biomicroscopy by using 90D lens
- Goldmann's applanation tonometry
- Indirect ophthalmoscopy by using 20D lens

Patient was recruited into the study if they had clinical features as described in standard diagnostic criteria by American Uveitis Society 1994[5]

STANDARD DIAGNOSTIC CRIETERIA FOR ACUTE REINAL NECROSIS[5]

The American uveitis society recommended diagnostic criteria to be used for all clinical and laboratory studies in acute retinal necrosis in the year 1994.

- Focal, well demarcated areas of retinal necrosis located in the peripheral retina (outside the major temporal vascular arcade).
- Rapid, circumferential progression of necrosis (if antiviral therapy has not administered)
- Presence of evidence of occlusive vasculopathy
- Prominent inflammatory reaction in vitreous and anterior chamber

Characteristics that support but not required for diagnosis are 1.optic atrophy 2.scleritis 3.pain.

Total clock hours of retinal necrosis detected in patients documented

INVESTIGATION: Patients after diagnosed to have Acute retinal necrosis clinically if needed investigated with USG B scan to rule out retinal detachment, ocular coherence tomography (OCT) to look for any macular involvement.

Few patients underwent vitreous tap and the vitreous sample was examined by polymerase chain reaction (PCR) to find herpes family virus like Varicella zoster, Herpes simplex 1 and Herpes simplex 2.First an uniplex PCR was done and followed by nested PCR.

Systemic investigation like Hemoglobin, total blood count, differential blood count, erythrocyte sedimentation rate, platelet count, urine analysis was done. ELISA for Human immunodeficiency virus was done to find patient's immune status with patients consent if needed.

Serial Fundus photography was taken to document the improvement of the disease after treatment.

TREATMENT: Patients was given oral antiviral therapy as a sole antiviral or combined antiviral therapy as per treating physician discretion. In Oral antiviral therapy, T.Valacyclovir 1000mg tds/ day was given for 8 to 12 weeks. Combined

antiviral therapy include a combination of oral antiviral along with intravitreal antiviral are oral antiviral along with intravenous antiviral and intravitreal antiviral. Intravitreal antiviral given in the form of Gancyclovir 2000µg in 0.1ml and intravenous antiviral as Inj.Acyclovir 5-10mg/kg tds/ day for 5days. All patients are treated with cycloplegic and T.Prednisolone 1mg/kg per day in titrated dose as per the response.

COMPLICATIONS AND ITS MANAGMENTS: The most common complication occurring in Acute retinal necrosis was RETINAL DETACHMENT. The time gap of occurrence of retinal detachment from onset of acute retinal necrosis was documented. The necrotic retina would mostly progress to detachment. The detachment would mostly be rhegmentogenous or Exudative. All the retinal detachment patient underwent vitreoretinal surgery with silicon oil tamponade.vitreo retinal surgery included 3 port pars plana vitrectomy, induction of posterior vitreous detachment if not already present, with or without sclera buckling and Endolaser to demarcate at the junction of normal and necrotic retina was done and silicon oil implantation was done. Patient vision at the time of retinal detachment and vision after vitreoretinal surgery was recorded. Mean time gap of silicon oil removal was documented and occurrence of re-retinal detachment following silicon oil removal was recorded.

Occurrence of secondary glaucoma and fellow eye involvement was documented. Mean time gap of involvement of fellow eye was recorded.

FOLLOW UP: All patients followed up for 6 months. Visual acuity, intraocular pressure, and a complete ocular examination was carried out during all follow up visit Complication if any was documented and treated appropriately. At the end of six months final best corrected visual acuity was recorded.

DATA COLLECTION TECHNIQUE AND TOOLS

All data from primary source was collected by an individual interview, observation, and complete ophthalmic examination of the subjects as per the present proforma and any additional information like complication and its management was mentioned in detail. Later these primary data was entered in a Microsoft excel sheet for a complete database. Data was also collected from secondary sources like pubmed, medline and various other journals for comparison of the primary data.

STATISTICAL METHODS

Mean (SD) and frequency (percentage) was used for continuous and categorical variable respectively. Fisher's extract test or chi-square test was used to assess the difference between the categorical variable. Student t-test or Mann-

Whitney U test was used to test mean difference between the two continuous variables. P-value of less than 0.05 considered as statistically significant. All statistical analysis was done by statistical software STATA 11.0

RESULTS

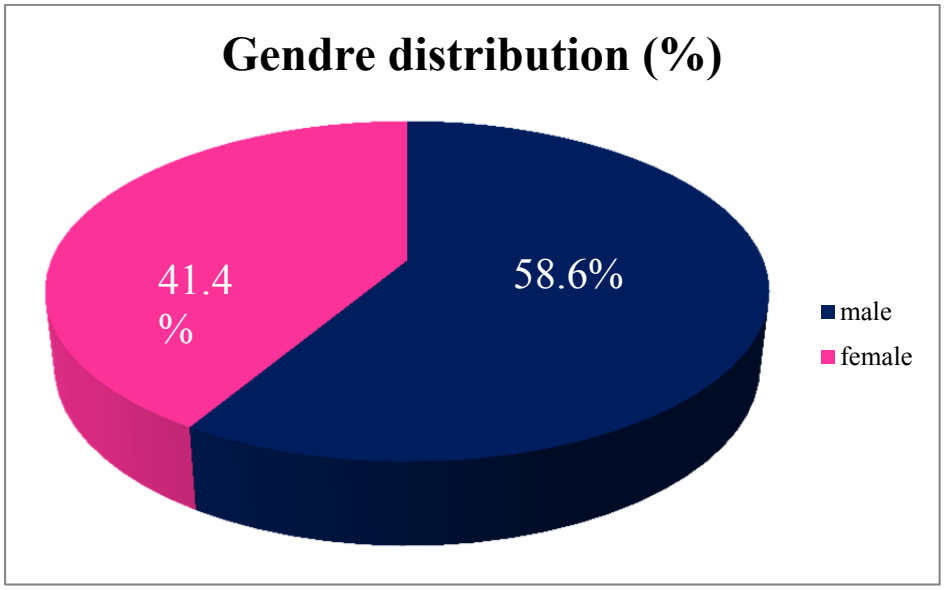
This study enrolled total of 29 patients and 31 eyes. Out of the 29 patients 1 patient died during the follow up period and 1 patient lost follow up. Therefore for end point observations results are calculated with 27 patients and 29 eyes.

1. TOTAL PATIENTS ENROLLED AND GENDER DISTRIBUTION

Table: 2

Gender	n(%)
Male	17 (58.6)
Female	12 (41.4)
Total	29(100)

Graph: 1



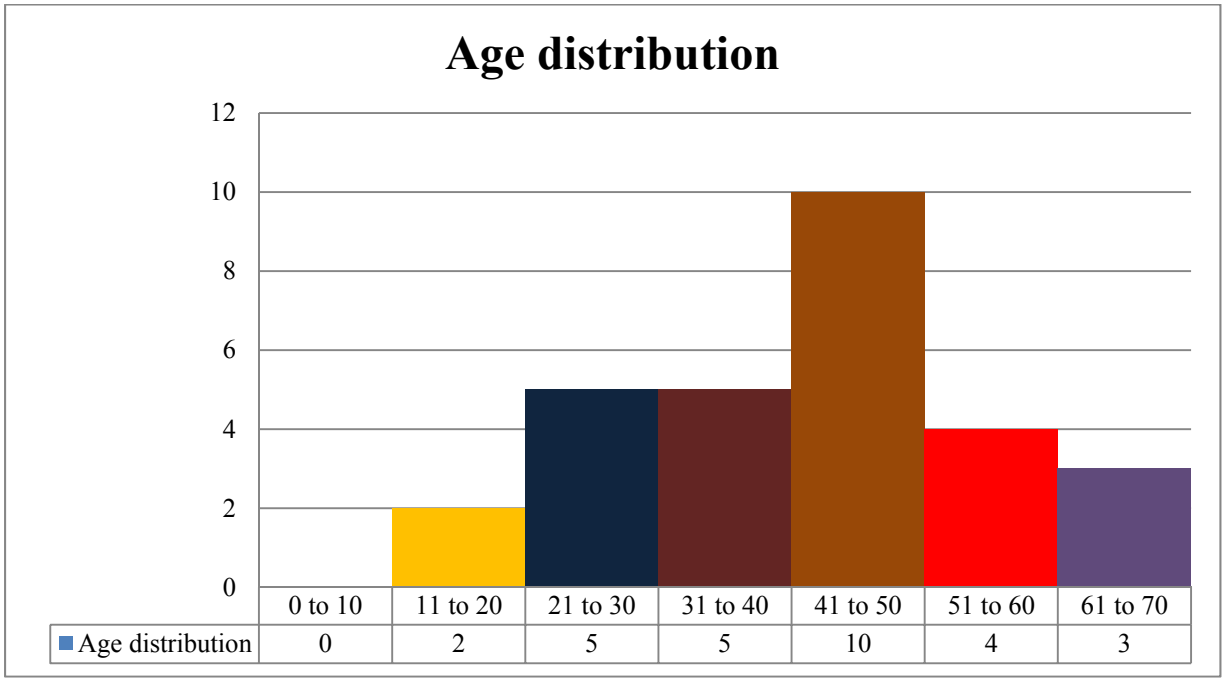
It was found that male had been affected more than female patient from our study. slight male preponderance was noted.

2. AGE DISTRIBUTION

Table: 3

Age	n	Mean(SD)	Min - Max
	29	42.1 (13.7)	18 - 65

Graph: 2



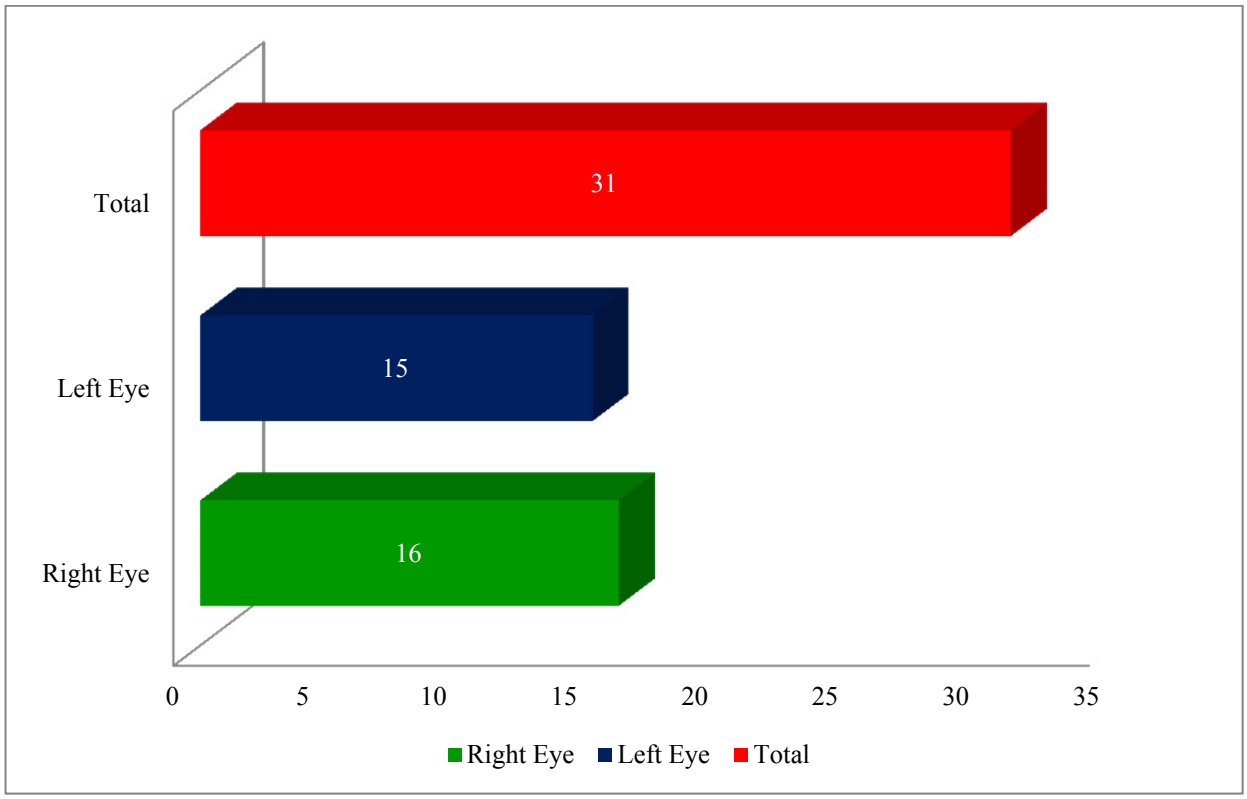
Minimum age of presentation was 18 years and maximum was 65 years. Mean age was 42.1 years with ± 1SD = 13.7. Our study also revealed bimodal peak in age of presentation with 3 patients between 16-25 age group and 13 in 45-65 age group. 16 patients out of 29 are between these two age group.

EYES STUDIED AND LATERALITY

Table: 4

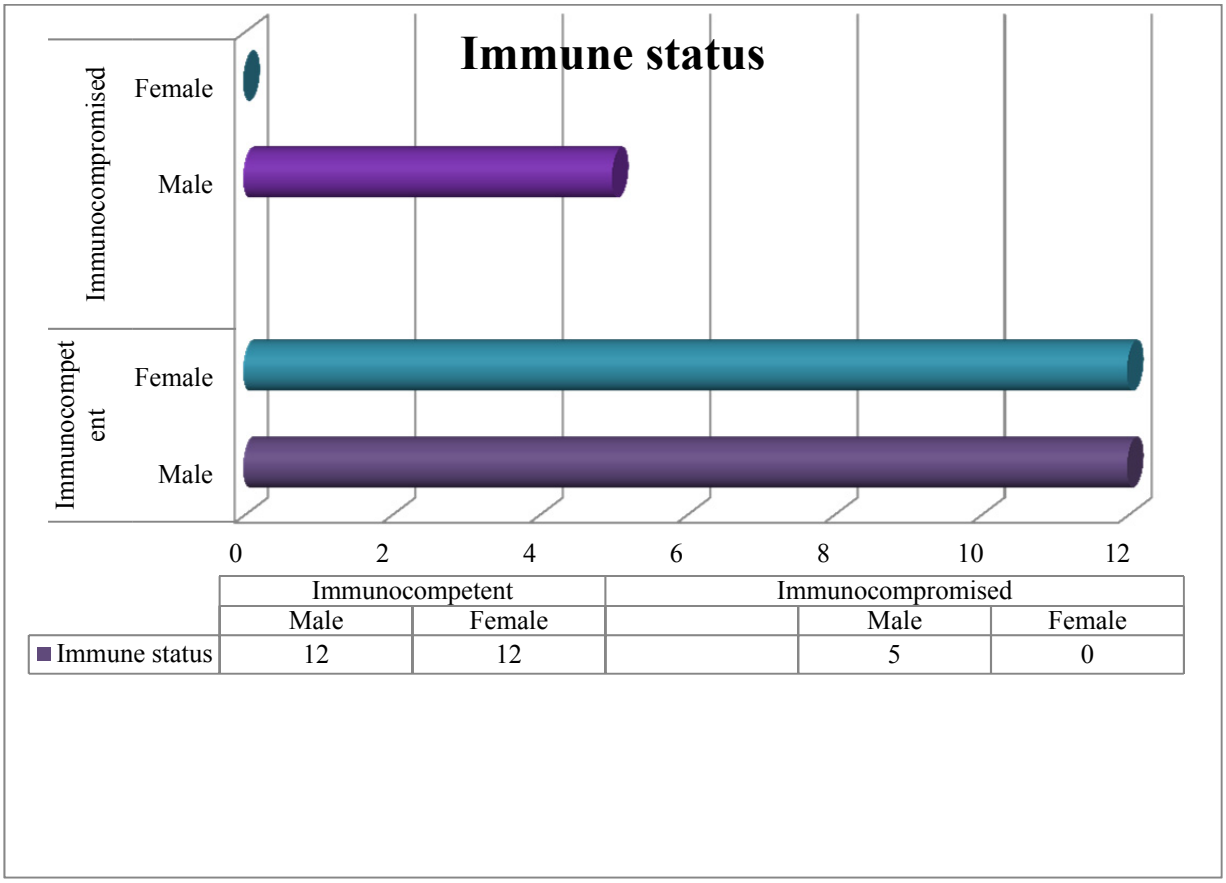
Eye	n(%)
Right eye	16 (51.6)
Left eye	15 (48.4)
Total	31(100)

Graph: 3



3. ANALYSIS OF IMMUNE STATUS AMONG PATIENTS

Graph: 4



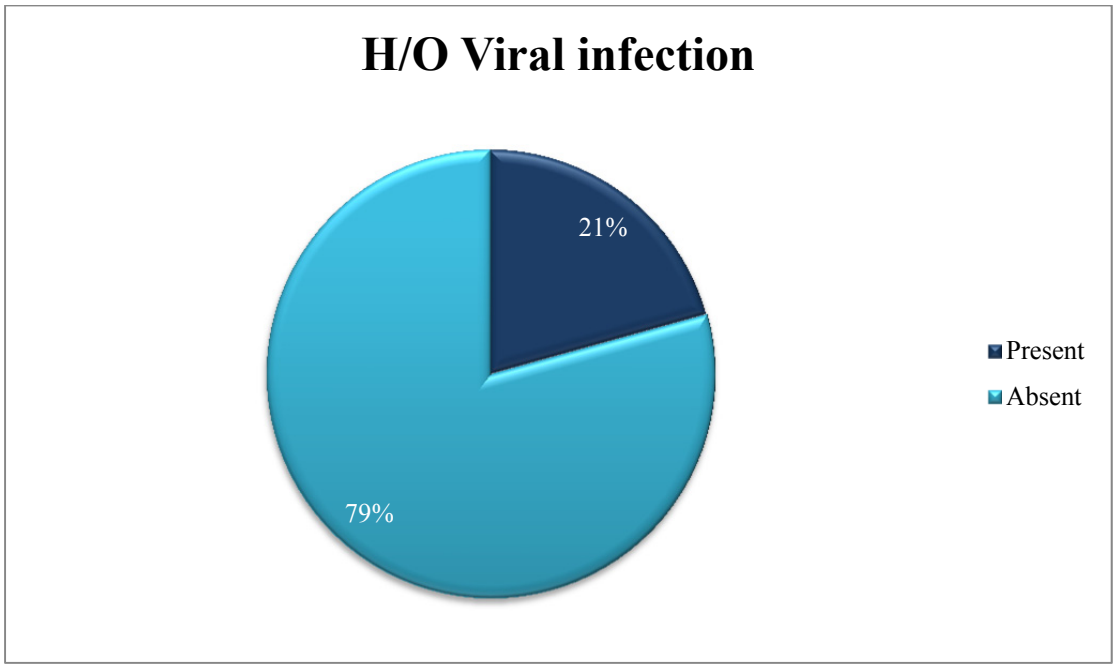
Totally 5 patients out of 29 patient are affected with AIDS (Acquired Immune Deficiency Syndrome). All 5 patients were males. Out of 5 immunocompromised patients one patient died during the follow up period.

4. HISTROY OF VIRAL INFECTION

Table: 5

Viral infection	n(%)
Yes	6 (20.7)
No	23 (79.3)
Total	29(100)

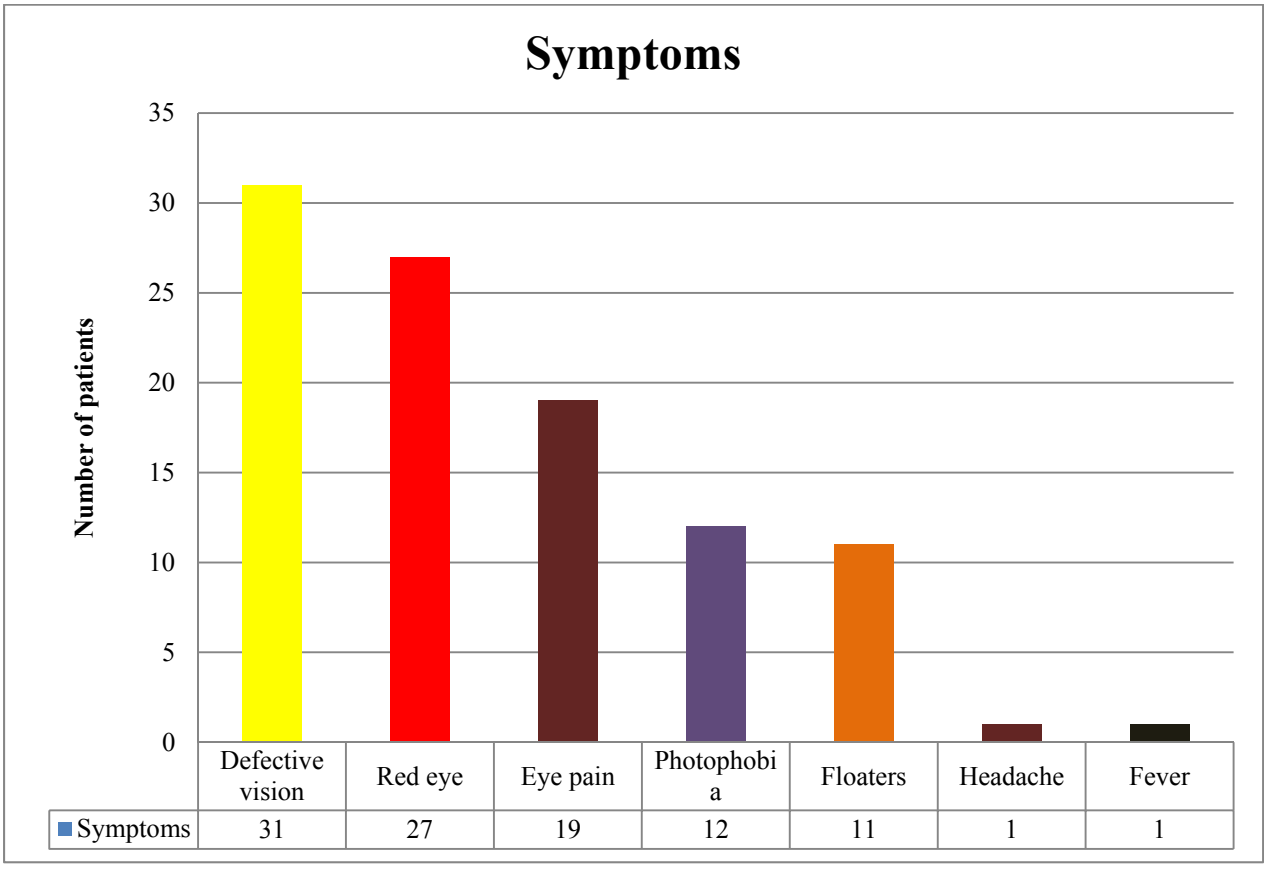
Graph: 5



Previous history of viral infection was given by 6 patients (20.7%). The most common viral infection being chicken pox seen 3 patients (50%).herpes zoster ophthalmicus in 1 patient (16.67%), viral keratitis in 1 patient (16.67%) and shingles in 1 patient (16.67%).

5. ANALYSIS OF SYMPTOMS

Graph: 6



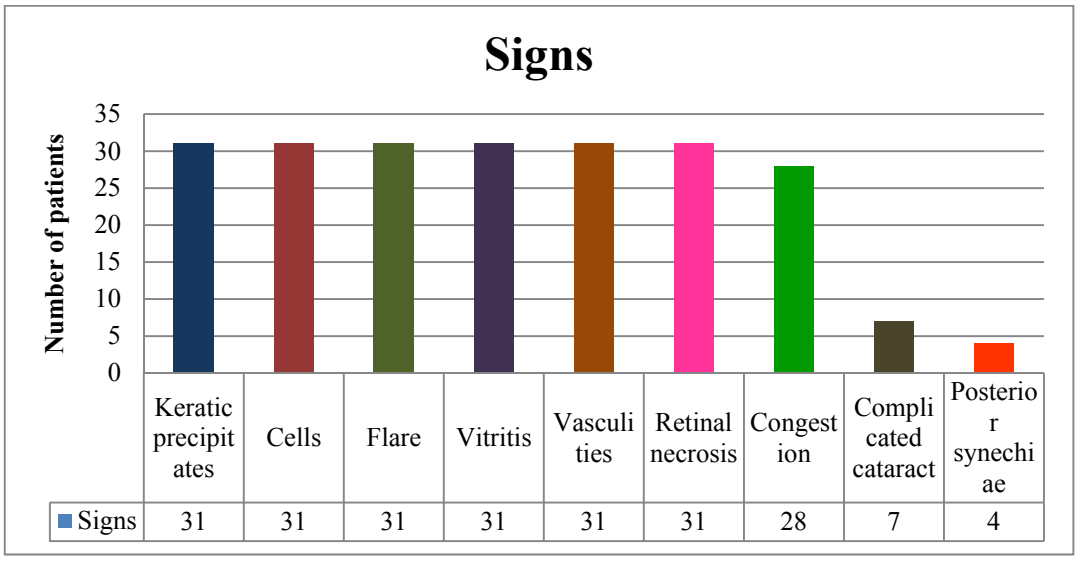
Most common symptom found was defective vision (100%) reported in all 31 eyes studied followed by redness of eyes (87.1%), ocular pain (61.3%), photophobia (40%), floaters (35.5%), headache (3.5%).

6. ANALYSIS OF SIGNS

Table : 6

Signs	n(%)
KPS	31 (100)
Cells	31 (100)
Flare	31 (100)
Vitritis	31 (100)
Vasculities	31 (100)
Retinal necrosis	31 (100)
Congestion	28 (90.3)
Complicated cataract	7 (22.6)
Posterior synechiae	4 (12.9)

Graph : 7



7. ANALYSIS OF MEAN CLOCK HOUR OF RETINAL NECROSIS

Table: 7

Treatment	n	Mean(SD)	Min - Max
Immunocompetent	24	5.2 (2.75)	2 -12
Immunocompromised	5	5 (2.82)	3 – 10
Clock Hour of ARN	31	5.12 (2.66)	2 -12

The mean clock hours of retinal necrosis observed was 5.12 clock hours, with minimum of 2 clock hours to maximum of 12 clock hours. The mean clock hour of retinal necrosis was found to be same (approximately 5 clock hours) between both immunocompetent patient and immunocompromised.

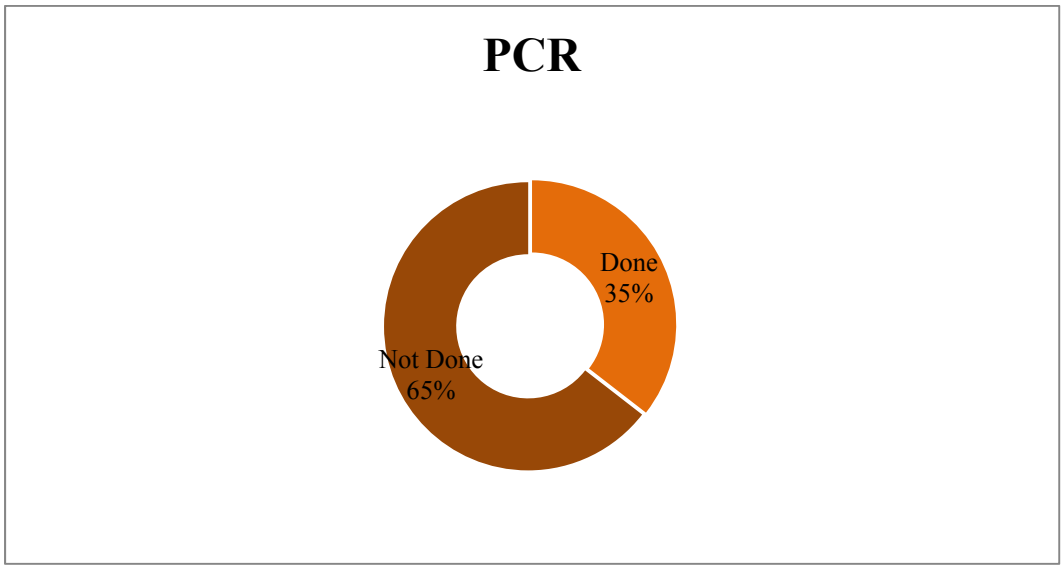
8. STUDY OF VIRUS FROM POLYMERASE CHAIN REACTION

Table: 8

PCR	n(%)
Done	11 (35.5)
Not done	20 (64.5)
Total	**31(100)**

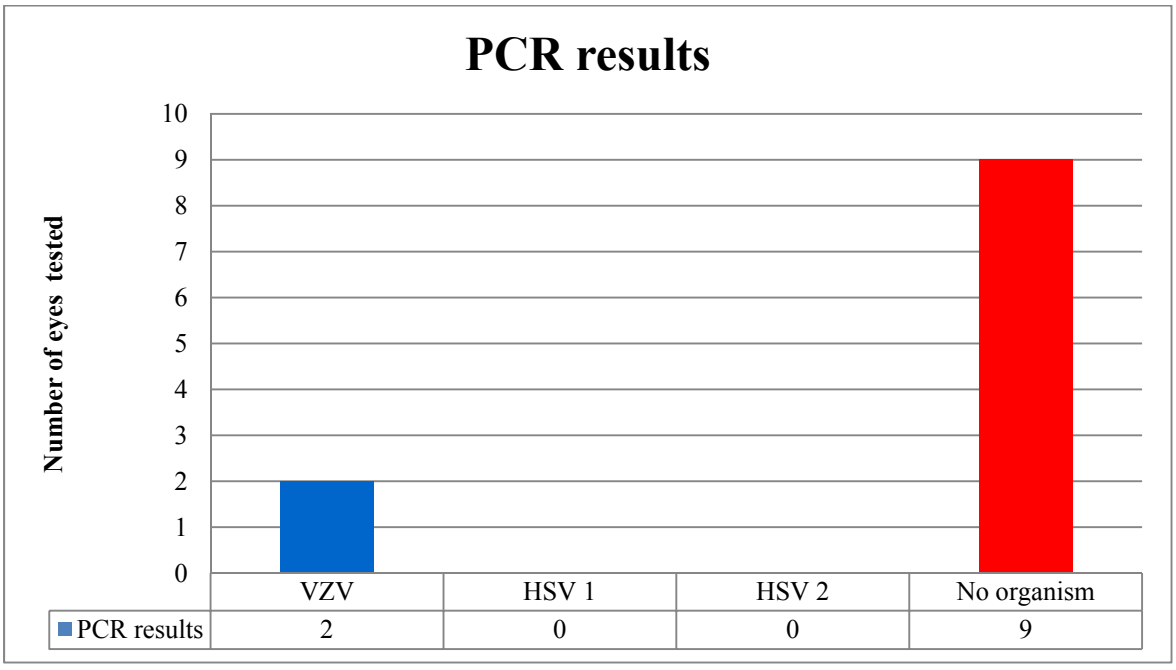
Vitreous sample of 11 patients was analyzed for herpes family virus through polymerase chain reaction

Graph: 8



9. RESULT OF POLYMERASE CHAIN REACTION

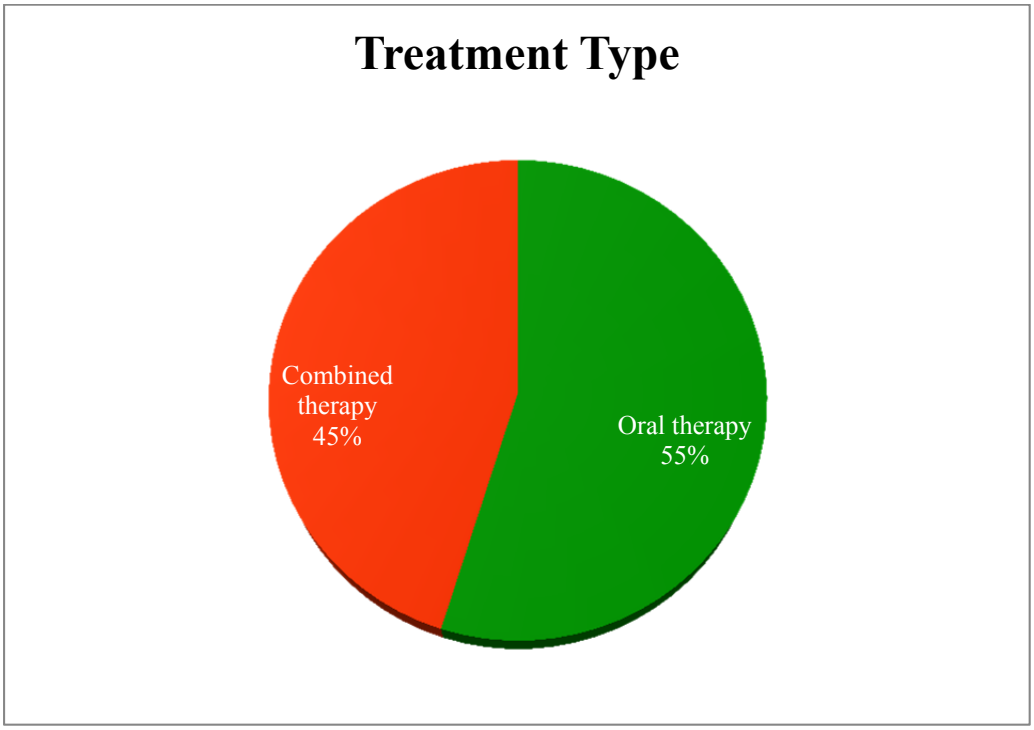
Graph: 9



Varizella zoster was detected in 2 patients (18.18%) and in 9 patients no organism could be detected.

10.ANALYSIS PATIENTS TREATED WITH ORAL ANTIVIRAL AND COMBINED ANTIVIRAL.

Graph: 10



Out of total 31 eyes, 17 eyes(55%) treated with sole oral antiviral and 14 eyes (45%) treated with combined antiviral therapy.

11.ANALYSIS OCCURRENCE OF RETINAL DETACHMENT

A. OVERALL OCCURRENCE OF RETINAL DETACHMENT

Graph: 11

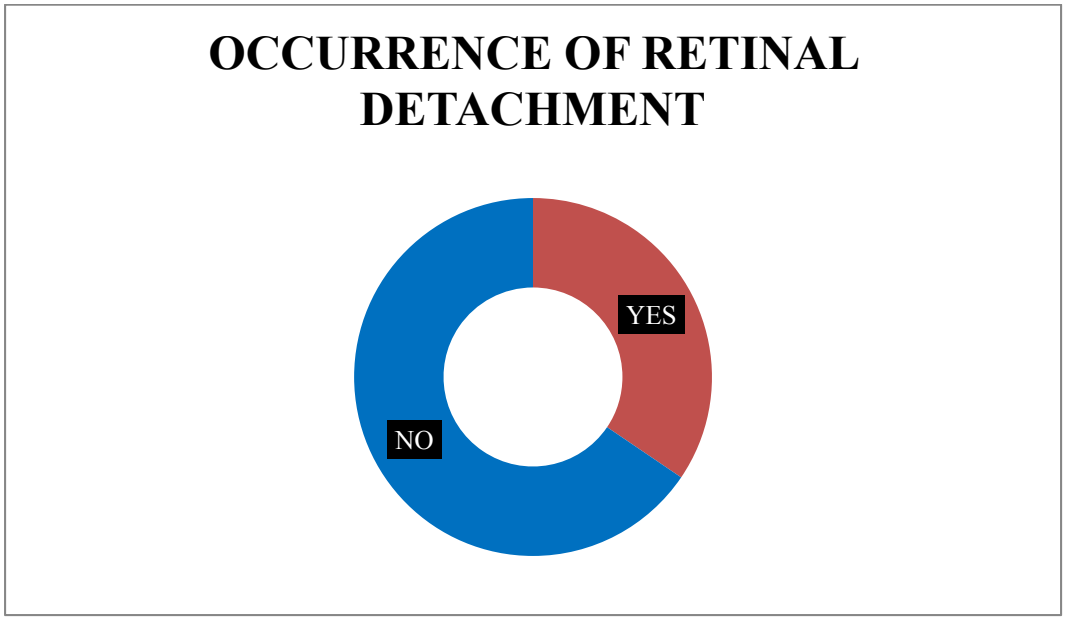


Table: 9

Occurrence of RD	n (%)
Yes	10 (34.4)
No	19 (65.6)

Total 29 eyes, 34.4% (10 eyes) suffered retinal detachment and 65.6% (19 eyes) did not proceeded to retinal detachment.

B. MEAN TIME GAP OF OCCURRENCE OF RETINAL DETACHMENT

Table: 10

Mean time gap of Occurrence of RD (weeks)	n	Mean	Min - Max
	29	4.2	At presentation- 14

Mean time gap of occurrence of retinal detachment was found to be 4.2 weeks, which varied from occurrence of retinal detachment at presentation to as long as 14 weeks.

C. ANALYSIS OF RETINAL DETACHMENT BETWEEN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS.

Table: 11

Immune status	RD occurrence		Total	P value^
	YES (%)	NO (%)		
Immuno competent (%)	8 (33.34)	16 (66.66)	24 (100)	0.613
Immuno compromised (%)	2 (40.00)	3 (60.00)	5 (100)	
Total	10 (34.40)	19 (65.60)	29 (100)	

^ Fisher's exact test

The progression to retinal detachment in comparison between immunocompetent (33.34%) and immunocompromised (40%) was much similar,

and no statistical significance(P= 0.613) was derived in between the two groups regarding progression of retinal detachment.

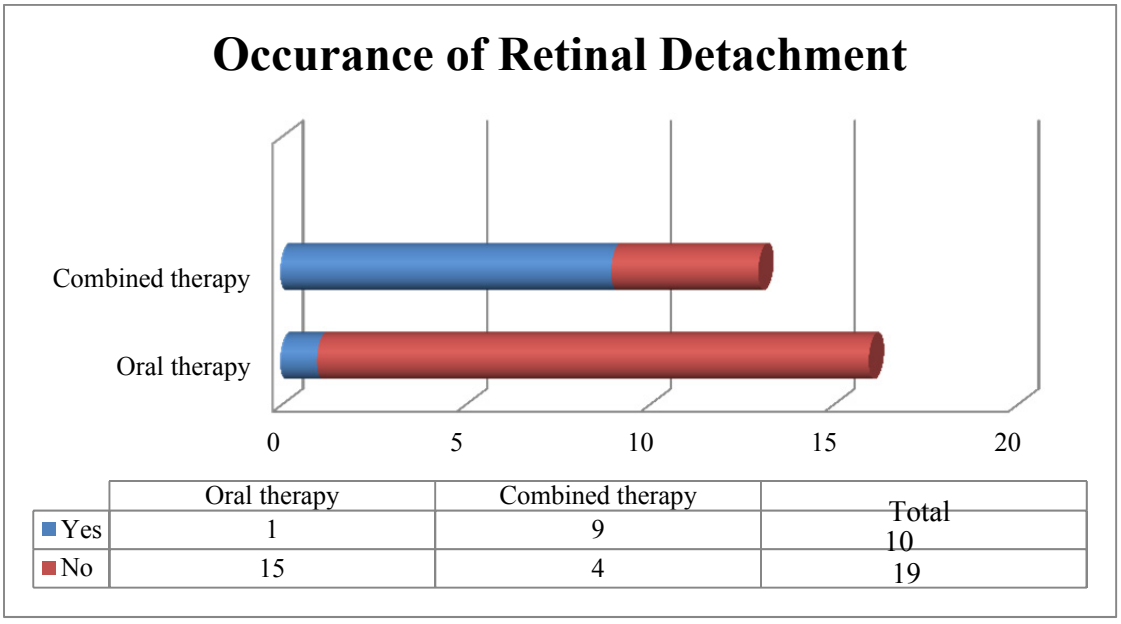
D. OCCURRENCE OF RETINAL DETACHMENT BETWEEN PATIENTS TREATED WITH ORAL AND COMBINED ANTIVIRAL THERAPY.

Table: 12

Treatment	Occurrence of RD		Total	P value^
	Yes(%)	No (%)		
Oral therapy (%)	1 (6.25)	15 (93.75)	16 (100)	0.001
Combined therapy (%)	9 (69.23)	4 (30.77)	13 (100)	
Total	10 (34.48)	19 (65.52)	29 (100)	

^ Fisher's exact test

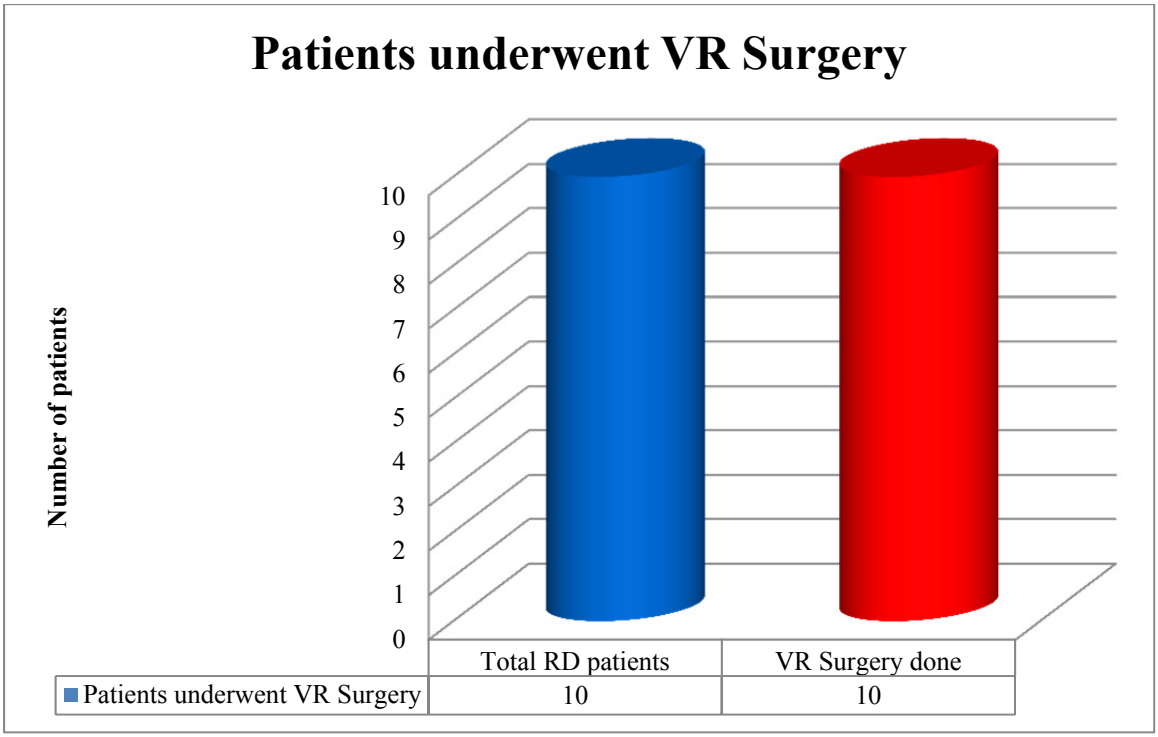
Graph: 12



Occurrence of retinal detachment in combined therapy 69.3% (9 eyes out of 16 eyes) and in oral antiviral therapy group was 6.25% (1 out of 16 eyes). There exist a statistical significance (P= 0.001) in occurrence of retinal detachment between oral therapy group and combined antiviral group.

E. VITREO RETINAL SURGERY DONE TO REATTACH RETINA.

Graph: 13



All 10 patients suffered retinal detachment underwent vitreo retinal surgery with silicon oil implantation.

F. SILICON OIL REMOVAL AND MEAN TIME OF REMOVAL

Table: 12

Silicon Oil Removal (SOR)	n (%)
Yes	7(70.0)
No	3(30.0)
Total	**10(100.0)**

Table: 13

Silicon Oil Removal Duration(months)	n	Mean(SD)	Min - Max
	7	3.29(0.76)	2-4

7 out 10 eyes (70%) underwent silicon oil removal with in the 6 months follow up period. Mean months of silicon oil removal done on 3.29 months ±0.76 (1 SD). With minimum of 2 months and maximum of 4 months.

G. RE-RETINAL DETACHMENT AFTER SILICON OIL REMOVAL.

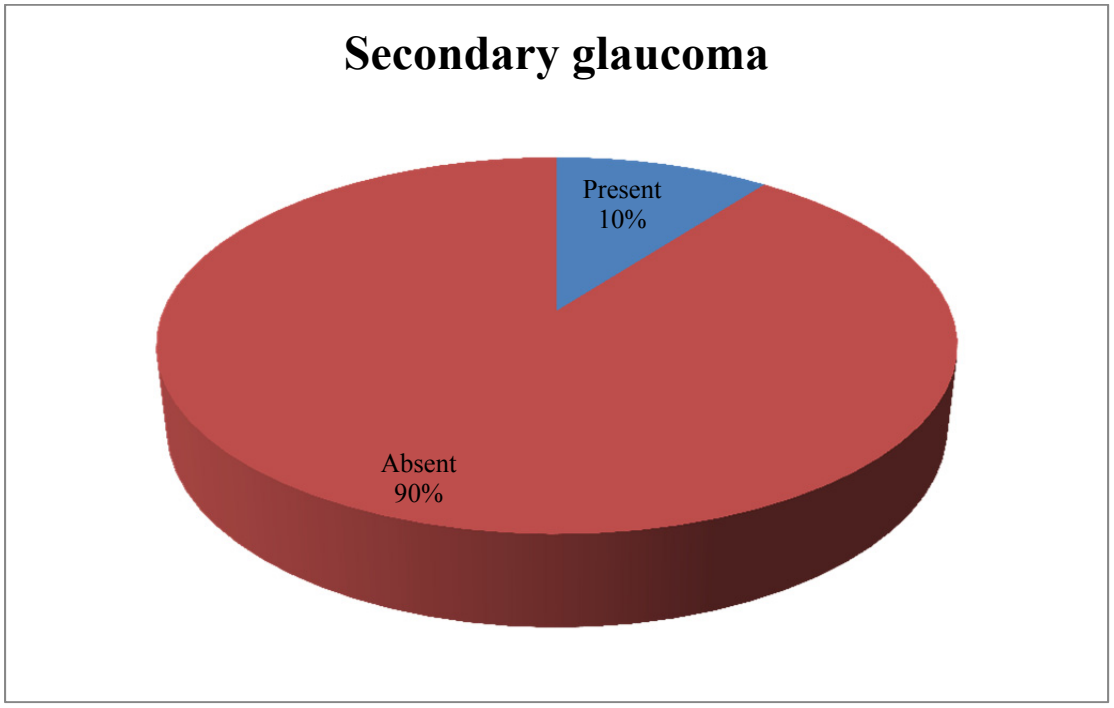
Table: 14

RE RD After SOR	n(%)
Yes	2(28.6)
No	5(71.4)
Total	**7(100.0)**

Re retinal detachment occurred in 28.6% eyes (2 eyes) on silicon oil removal.

12.OCCURRENCE OF SECONDARY GLAUCOMA

Graph: 14



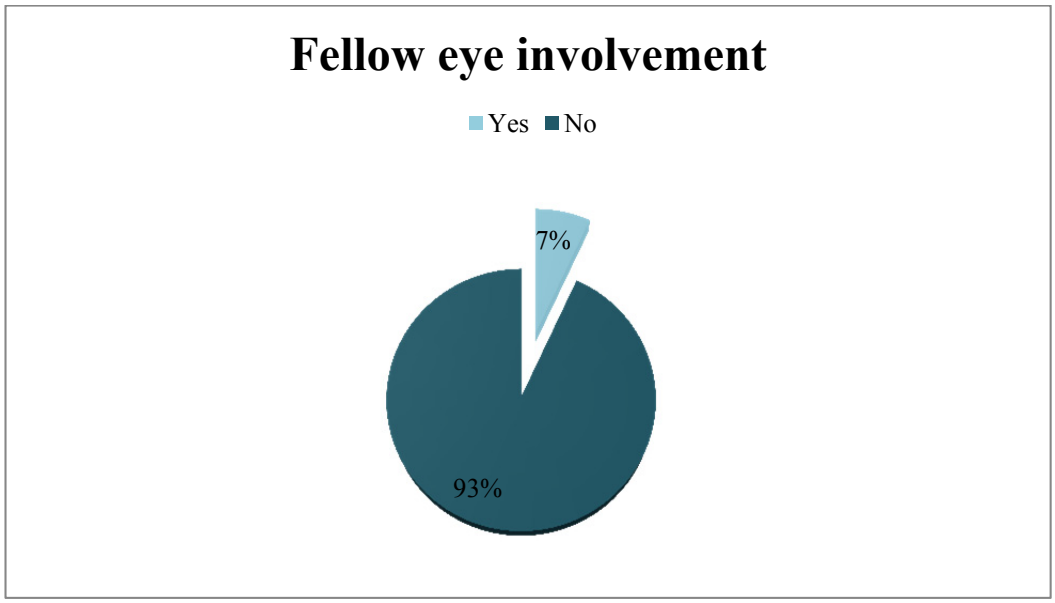
3 eyes out of 29 (10%) progressed to secondary glaucoma.

13.ANALYSIS FELLOW EYE INVOLVEMENT

Table: 15

Mean time gap of fellow eye involvement (weeks)	n	Mean	Min - Max
	2	2.5	2- 3

Graph: 15



2 patient out 29 had fellow eye involvement, with mean time gap of involvement being 2.5 weeks.

14.VISION ANALYSIS

A. OVERALL VISION ACUITY ANALYSIS BETWEEN INITIAL AND FINAL.

Table: 16

Visual Acuity	n	Mean (Snellen's Equivalent)	SD	Median	P value#
Initial	31	0.96 (6/55)	0.70	0.78	0.002
Final	29	0.69 (6/30)	0.60	0.48	

Wilcoxon sign rank test

The over all mean initial acuity in 31 eyes was 0.96LogMar±0.70 (1SD), mean final visual acuity in 29 eyes was 0.69LogMar±0.60 (1SD). On analysis if was found there exist a statistically significant (P=0.002) improvement in vision at the end of six months of treatment.

B. VISION ANALYSIS BETWEEN ORAL AND COMBINED THERAPY

Table: 17

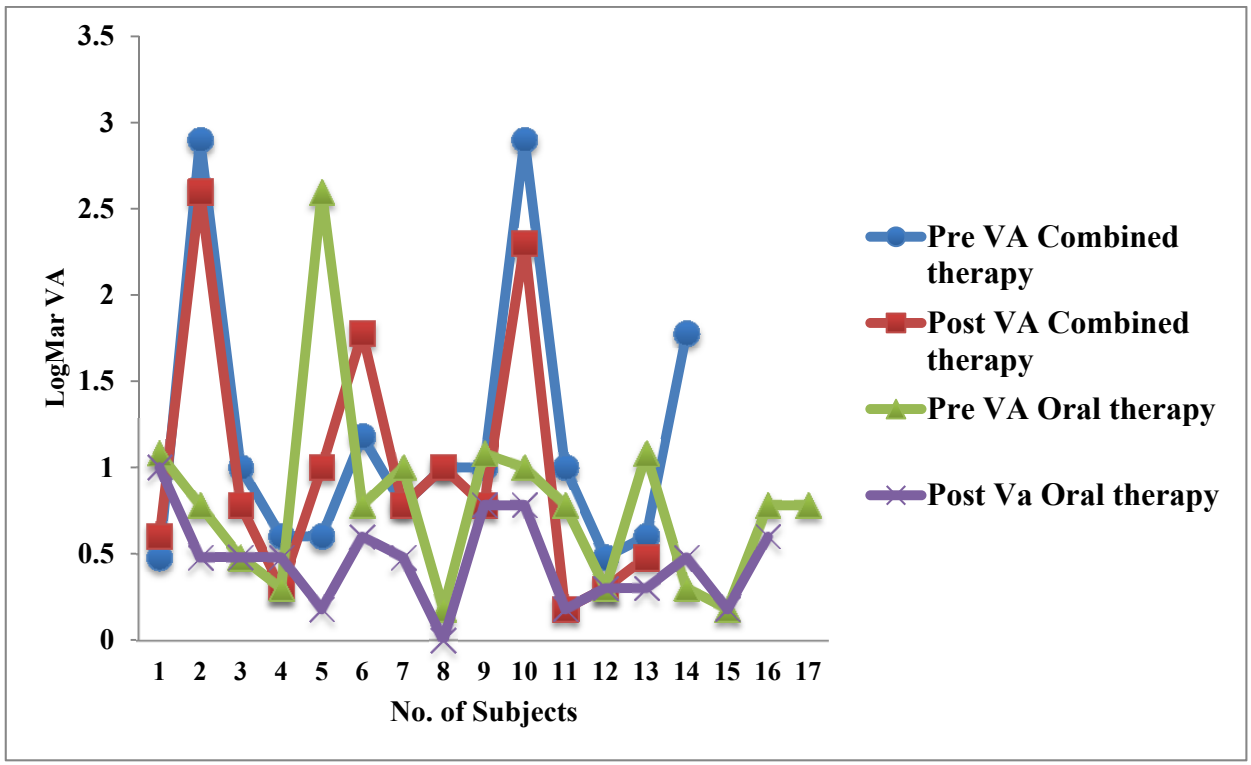
Treatment	**n (%)**	**Initial**		**Final**		**P value**
		Mean (SD)	***Median (Min – Max)***	***Mean (SD)***	***Median (Min – Max)***	
Oral therapy	17 (54.8)	0.79 (0.57)	0.78 (0.18 – 2.60)	0.46 (0.26)	0.48 (0 – 1.00)	0.006*
Combined therapy	14 (45.2)	1.16 (0.81)	1.00 (0.48 – 2.90)	0.99 (0.76)	0.78 (0.18 – 2.60)	0.183*
P value	-	0.193#	-	0.026#	-	-

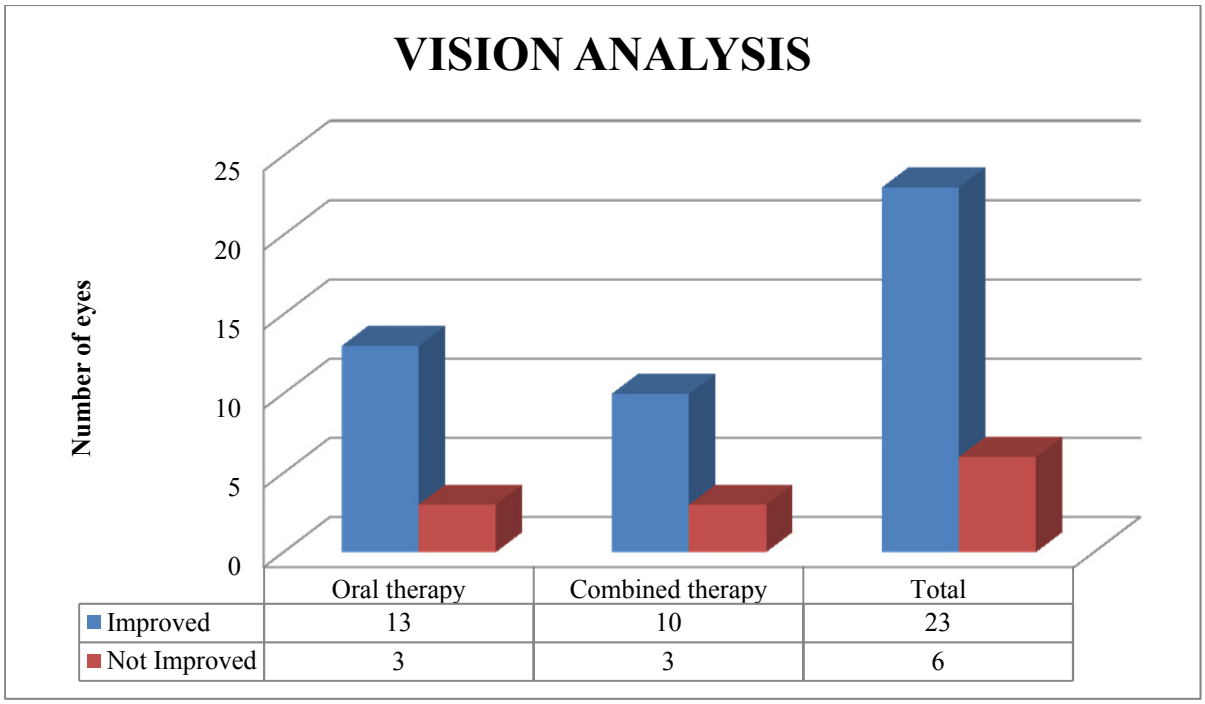
Mann Whitney U test ;*- Wilcoxon Sign rank test

The mean initial visual acuity in oral antiviral therapy group was 0.79LogMAR±0.57 (1SD) and mean final visual acuity was 0.46±0.26 Log Mar. A statistically significant (P=0.006) improvement in visual acuity between initial and final vision in oral therapy. No statistical significant (P=0.183) improvement in visual acuity was noted between initial (mean= 1.16LogMar±0.81 (1SD)) and final visual acuity (mean 0.99±0.76 LogMar) in combined antiviral therapy group.

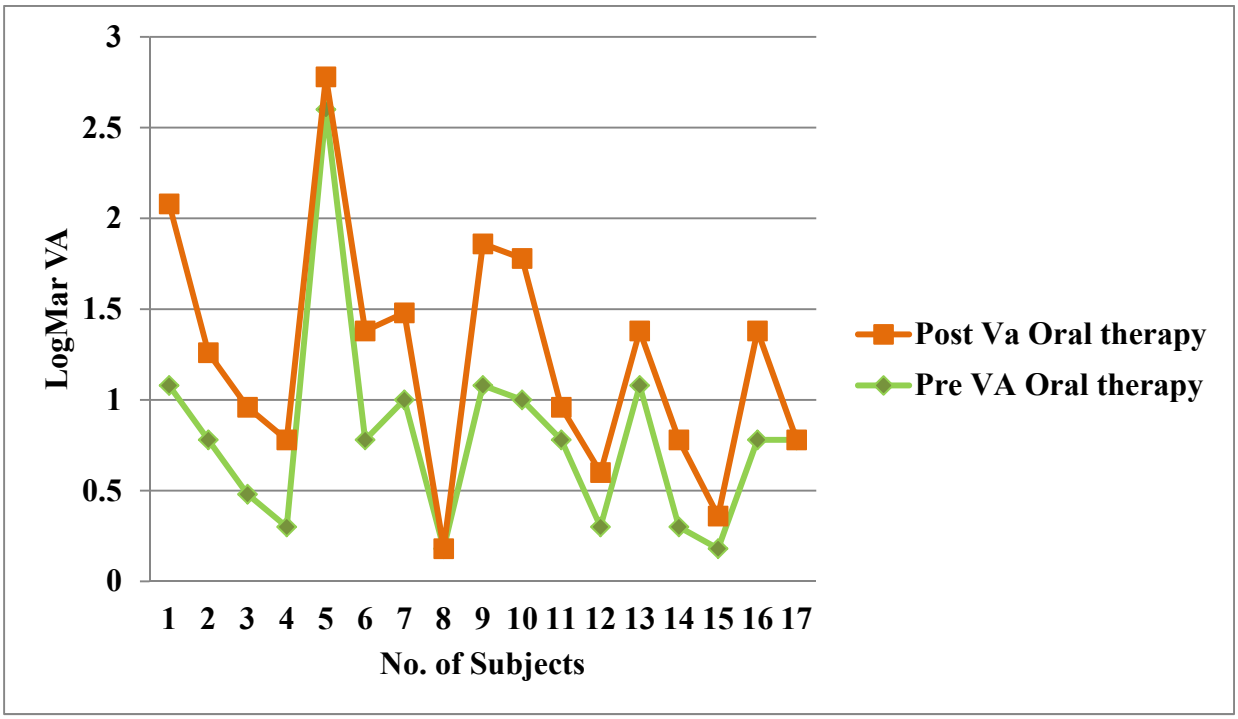
There exists a statistical significant difference (P=0.026) between final vision between oral antiviral and combined antiviral group with oral antiviral therapy group had better final visual acuity.

Graph:16

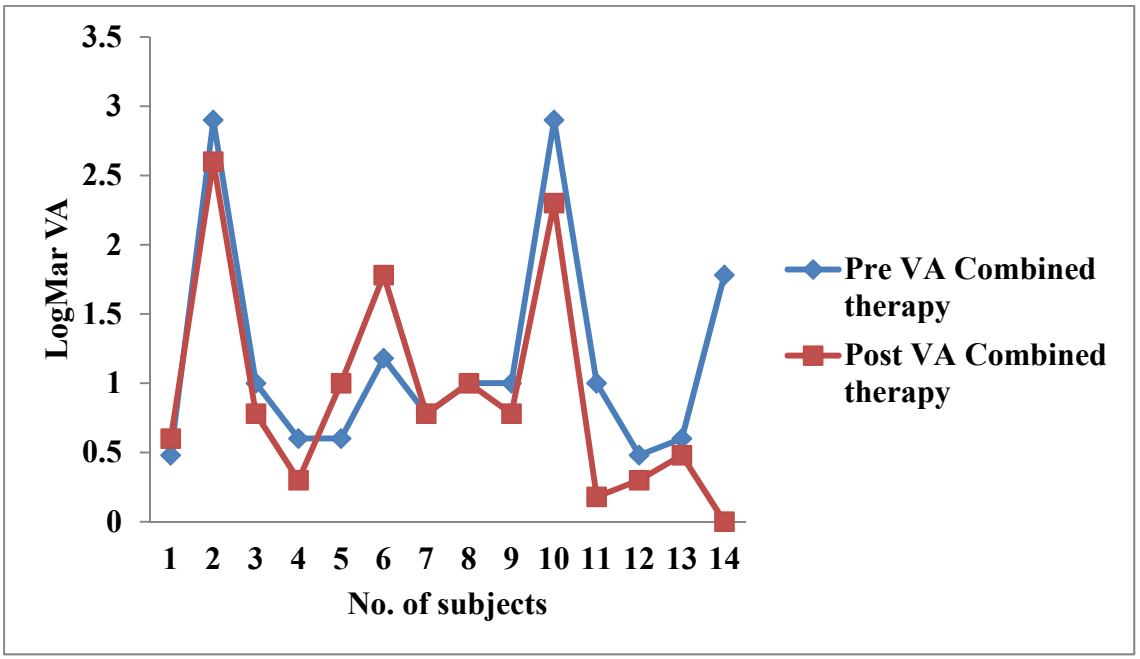



VISION ANALYSIS
Number of eyes
25
20
15
10
5
0
Oral therapy
Combined therapy
Total
Improved
13
10
23
Not Improved
3
3
6

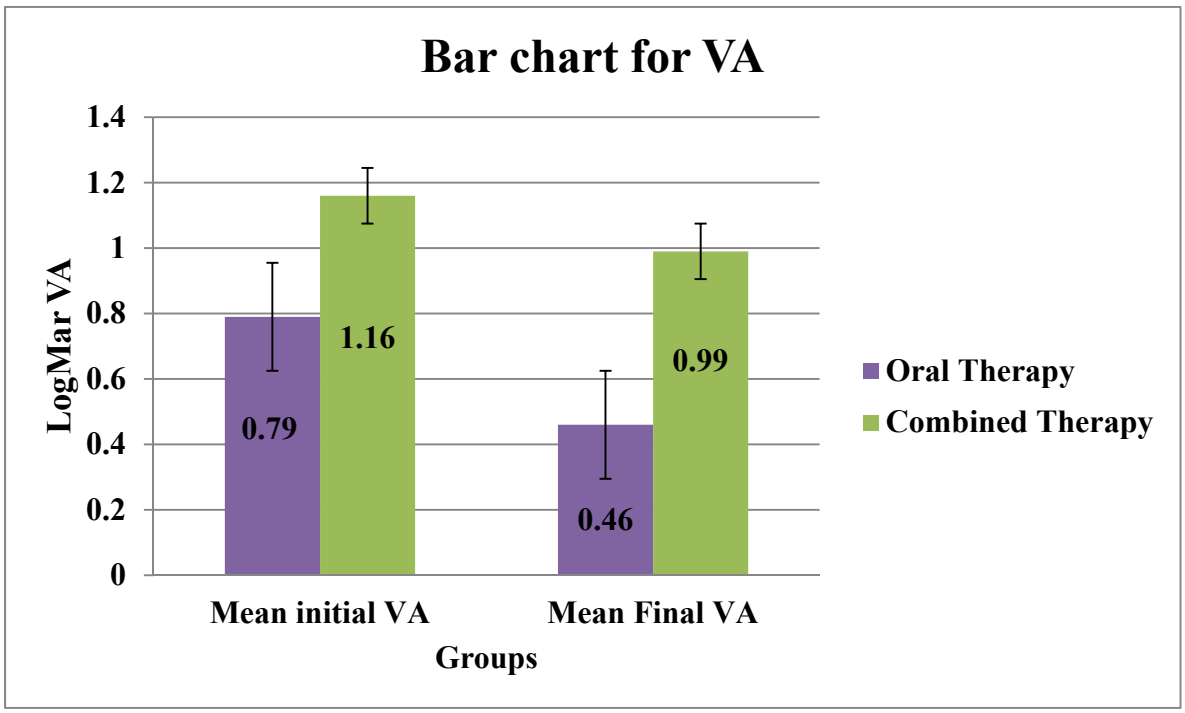
Graph: 17


LogMar VA
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
No. of Subjects
Post Va Oral therapy
Pre VA Oral therapy

Graph: 18



Graph: 19



C. ANALYSIS OF VISUAL ACUITY BETWEEN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS.

Table: 18

Immune Status	n	Initial		n	Final		P value
		Mean (SD)	*Median (Min – Max)*		*Mean (SD)*	*Median (Min – Max)*	
Immuno competent	24	0.86 (0.69)	0.78 (0.18 – 2.90)	23	0.71 (0.66)	0.48 (0 – 2.60)	0.037*
Immuno compromised	5	1.14 (0.38)	1.08 (0.78 – 1.78)	4	0.76 (0.21)	0.78 (0.48 - 10)	0.060*
P value	-	0.050#		-	0.250#		-

Mann Whitney U test ;*- Wilcoxon Sign rank test

Visual acuity improved with statistically significant (P=0.037) between initial and final visual acuity in immunocompetent patients. An improvement in vision is noted between mean initial and final visual acuity in immunocompromised patients, but not statistically significant (P=0.060)

D. ANALYSIS OF VISUAL ACUITY BEFORE AND AFTER VITREO RETINAL SURGERY FOR RETINAL DETACHMENT.

Table: 19

Vision in RD surgery Patients	n	Mean (1SD)	Median (Min - Max)	P value
Before	10	1.46 (0.89)	1.00 (0.48 – 2.90)	0.059#
Final	10	1.09 (0.69)	1.00 (0.30 – 2.60)	

Wilcoxon Sign rank test

The mean visual acuity before surgery was 1.49±0.89 LogMar and final mean visual acuity was 1.09±0.69 LogMar. There was improvement in vision after surgery but not statistically significant (P= 0.059).

DISCUSSION

Acute retinal necrosis is an potential vision threatening condition, prompt diagnosis and treatment is a must to preserve vision and prevent complications.

DEMOGRAPHIC ANALYSIS.

GENDER: Our study reveals that there exists no gender prelidiction between males and females in occurrence of acute retinal necrosis, but a slight male preponderance was observed as reported in various literature.

STUDY	MALES	FEMALES
Muthiah et al[23]	71%	29%
Cochrane et al[20]	55.6%	44.4%
Flaxel et al[9]	42%	58%
Our study	58.6%	41.4%

AGE: The mean age of occurrence of acute retinal necrosis in our study was 42.1 years, this is in accordance to Meghpara et al [28]they reported the mean age group to be 42 years. As reported by Blumenkranz et al[8] there exist a bimodal distribution in ages of affected patients. With 3patients in 16-25 age group and13 patients in 45-60 age group. Out of 29 patients reported 16 patients are in this two

age group. the minimum age reported in our study was 18 years and maximum was 65 years.

IMMUNE STATUS: All patients with history of AIDS are considered immunocompromised. All immunocompromised patients reported in our study was males and one patient died during the follow up period.Our study reveals acute retinal necrosis is more common in immunocompetent patient than in immunocompromised patients. Previous studies also reported similar findings.

STUDY	IMMUNOCOMPROMISED	IMMUNOCOMPETENT
Muthiah et al[23]	23%	77%
Cochrane et al[20]	28%	72%
Our study	17.2%	82.8%

HISTORY OF VIRAL INFECTION: History of viral infection was found in 20.7% of patients in our study.

STUDY	H/O VIRAL INFECTION
Cochrane et al[20]	55.6%
Meghpara et al[28]	45%
Flaxel et al	38%
Our study	20.7%

The most common viral infection reported was chickenpox(50%) followed by herpes zoster ophthalmicus, shingles and viral keratitis (each 16.67%).No history of other herpes infection like HSV meningitis, genital ulcers was reported. Various other studies too reported chicken pox was the commonest viral infection preceded Acute retinal necrosis.

STUDY	CHICKEN POX	HZO	SHINGLES	VIRAL KERATITIS
Cochrane et al [20]	20%	13.3%	-	4.4%
Muthiah et al[23]	70.6%	20.7%	-	9.7%
Flaxel et al[9]		18%	9%	18%
Our study	50%	16.67%	16.67%	16.67%

SYMPTOMS: Acute retinal necrosis present with varied symptoms, the most common symptom reported was sudden defective vision in the eye involved. In our study all 29 patient complained of defective vision. Other symptoms reported in our study was redness of eyes, ocular pain, photophobia, floaters, head ache and fever.

STUDY	DEFECTIVE VISION	RED EYE	OCULAR PAIN	PHOTOPHOBIA	FEVER
Muthiah et al [23]	85.1%	26.1%	25.8%	54.5%	16.1%
Our study	100%	87.1%	61.3%	40%	3.5%

ARN is an blinding disease, it presents as sudden defective vision and patients should report to an ophthalmologist as soon as possible to get treated and there by prevent from detoriation of vision. Ophthalmologist too should be prompt in diagnosis of acute retinal necrosis and to treat the disease effectively to prevent patients from this blinding disease.

SIGNS: Acute retinal necrosis present with both anterior as well as posterior segment features. We as ophthalmologist must examine the patients meticulously. A complete detailed torch light examination, slit lamp examination and indirect ophthalmoscopic examination should be carried out. Prompt diagnosis and treatment of the disease would prevent this blinding disease.

The most common sign reported in our study was Granulomatous keratic precipitates, cells usually ranged from +1 to +3, flare in aqueous humour, vitritis, retinal vasculitis and retinal necrosis. All the above mentioned signs are seen in all patients (100%). Congestion was seen in 90.3%, complicated cataract seen in 22.6% and posterior synechae seen in 12.9% of patients.

Muthaiah et al [23] reported anterior segment signs in 80.6% of patients and vitritis seen in 83.6% of patients. Lau et al [17] reported 6.81% of patients developed complicated cataract.

RETINAL NECROSIS: Retinal necrosis is the hall mark of Acute retinal necrosis, the necrosis occurs in typical pattern as (i) Focal, well demarcated areas of retinal necrosis located in the peripheral retina (outside the major temporal vascular arcade). (ii)Rapid, circumferential progression of necrosis (if antiviral therapy has not administered). The mean clock hours of retinal necrosis found in our study was 5.12±2.66 clock hours. The mean extend of retinal necrosis was similar in both immunocompetent (5.2 clock hours) and immunocompromised patients (5.0 clock hours). Extend of necrosis was between 2 clock hours has minimum and 12 clock hours as maximum. Hillenkamp et al [24] reported a mean retinal necrosis to be 9.1 clock hours in his study.

POLYMERASE CHAIN REACTION (PCR): In recent year the introduction of polymerase chain reaction for both quantitative and qualitative analysis of virus had revolutionized the diagnosis of acute retinal necrosis. Classification of ARN was proposed by Flaxel et al [9]based on isolation of virus from ocular fluid sample. Definite *ARN* is defined as in patients with features of ARN as per standard diagnostic criteria with herpes virus DNA confirmation from aqueous or vitreous sample through PCR.

Few patients in our study underwent vitreous tap and the collected vitreous sample was analyzed for VZV, HSV 1 and HSV 2 through polymerase chain reaction. First an uniplex PCR is done and then a nested PCR is done for the sample. In our study 11 eyes out of 31(35.5%) underwent vitreous tap for viral DNA analysis through PCR. Like various other studies, our study to found that Varicella zoster virus was the commonest virus detected. It was also inferred that PCR positivity rate in our study was comparatively lower than other studies

STUDY	PCR positivity	VZV	HSV
Muthiah et al[23]	89%	-	-
Cochrane et al[20]	86.4%	62.5%	25%
Flaxel et al[9]	78.57%	18%	45%
Lau et al [17]	86.7%	66%	22%
Our study	35.5%	18.18%	0

TREATMENT: In our study, patients are treated with oral valacyclovir 1000mg per day (given for approximately 8 to 12 weeks) or treated with intravenous acyclovir 10mg/kg 3times per day for 5days and followed with oral valacyclovir 1000mg 3 times per day. Few patients in addition to intravenous and oral acyclovir also given intravitreal Ganciclovir 2000µg in 0.1ml.Patients treated with oral valacyclovir as the sole antiviral administered are grouped as oral therapy patients and patients treated with 2 or more route of antiviral are grouped as combined

therapy group. In our study 17 eyes of 31 (55%) treated with oral therapy and 45% of eye (14 eyes) treated with combined therapy. All patients in addition to antiviral received oral and topical prednisolone and cycloplegic. The treatment was administered as per the treating ophthalmologist discretion. Emerson et al in the year 2006 reported about treating ARN with oral valacyclovir/ famicyclovir, as sole antiviral. In our study no patients underwent prophylactic laser

RETINAL DETACHMENT: The necrosis over time would progress to retinal detachment. The detachment may Exudative, reghmentogenous or combination of above mentioned two factors. Our study reports over all occurrence of retinal detachment to be 34.4% (10 out of 29 eyes suffered RD. In comparison to literature collected, occurrence of retinal detachment was lower in our study.

STUDY	OCCURRENCE OF RD	TIME GAP OF OCCURENCE
Muthiah et al[23]	75%	-
Cochrane et al[20]	75%	4-11 weeks
Hillenkamp et al [40]	73%	6-84 days
Flaxel et al[9]	45%	3wk-5 months
Our study	34.4%	1day- 14 wks

MEAN TIME GAP OF OCCURRENCE OF RETINAL DETACHMENT was 4.2 week as found from our study.

The progression to retinal detachment in comparison between immunocompetent (33.34%) and immunocompromised (40%) was much similar, and no statistical significance (P= 0.613) was derived in between the two groups regarding progression of retinal detachment.

OCCURRENCE OF RETINAL DETACHMENT BETWEEN PATIENTS TREATED WITH ORAL AND COMBINED ANTIVIRAL THERAPY:

On analysis of patients suffered retinal detachment, it was found that oral therapy patients progressed to retinal detachment lesser (34.48%) as compared to combined therapy patients (65.52%). It was also found a statistically significance exists between both groups (P=0.001)

STUDY	GROUP	OCCURRENCE OF RD
Emerson et al [29]	Oral therapy	25%
Flaxel et al[9]	Combined therapy	28.57%
Our study	Oral therapy	34.48%
Our study	Combined therapy	34.48%

All 10 eye which progressed to retinal detachment, underwent vitreo retinal surgery (23G 3 port pars plana vitrectomy, endo laser at the junction of attached and retinal with necrosis and silicon oil tamponade with or without sclera buckle).

Silicon oil was removed in 7 out of 10 eyes. The mean time gap of removal was 3.29 weeks

Re retinal detachment occurred 2 out of 7 eyes(28.6%) in whom silicon oil was removed.

STUDY	ATTACHMENT ATTAINED	RE DETACHMENT OCCURRED
McDonald et al [33]	89%	11%
Our study	71.4%	28.6%

SECONDARY GLAUCOMA: It was found that 3 eyes out of 29 progressed to secondary glaucoma.

STUDY	SECONDARY GLAUCOMA
Lau et al[17]	33%
Our study	10%

FELLOW EYE INVOLVEMENT: 2 patient out of 29 had fellow eye involved, the mean time gap was 2.5 weeks

STUDY	FELLOW EYE INVOLVEMENT
Muthiah et al[23]	3.22%
Cochrane et al[20]	8.9%
Meghpara et al[28]	10%
Our study	10%

In our study no patients reported with optic atrophy and phthisis bulbi till six months of follow up period

VISION ANALYSIS: Acute retinal necrosis is an potential blinding disease. Protection of vision is primary aim in treatment of the disease. Patients vision was monitored in all visits. Best corrected visual acuity is recorded by Snellens chart and converted to LogMar scale for statistical analysis. Patients vision is said to be detoriated if his final vision is less than is vision at presentation and vision is said to be not detoriated if patients final vision at the end of six months follow up remained the same or improved in comparison to his initial vision at presentation.

The overall visual acuity of all eyes studied had improved significantly at the end of six month of treatment. Our study found that 23 eye(79.39%) vision had not deteriorated and in 6 eyes (28.61%) vision had deteriorated.

STUDY	VISION DETERIORATED	VISION NOT DETERIORATED
Muthiah et al[23]	44.1%	26.5%
Emerson et al[29]	25%	75%
Our study	28.61%	79.39%

Our study found the mean initial visual acuity in oral antiviral therapy group was 0.79LogMAR±0.57 (1SD) and mean final visual acuity was 0.46±0.26 LogMar. A statistically significant (P=0.006) improvement in visual acuity between initial and final vision in oral therapy. Cochrane et al [20] reported final mean visual acuity of patients treated with oral antiviral only was 0.89± 0.79 LogMar.

No statistical significant (P=0.183) improvement in visual acuity was noted between initial (mean= 1.16LogMar±0.81 (1SD)) and final visual acuity (mean 0.99±0.76 LogMar) in combined antiviral therapy group. Flaxel et al [9] reported in combined antiviral therapy mean visual acity improved from 1.01±0.61 LogMar to 0.59±0.51LogMar.

Visual acuity improved with statistically significant (P=0.037) between initial and final visual acuity in immunocompetent patients. An improvement in

vision is noted between mean initial and final visual acuity in immunocompromised patients, but not statistically significant (P=0.060)

The mean visual acuity before surgery was 1.49±0.89 LogMar and final mean visual acuity was 1.09±0.69 LogMar. There was improvement in vision after surgery but not statistically significant (P= 0.059).

STUDY	Post RD surgery Vn not deteriorated	Post RD surgery Vn deteriorated
McDonald et al[33]	78%	22%
Lau et al[17]	33%	67%
Muthiah et al[23]	40%	60%
Our study	90%	10%

LIMITATIONS IN OUR STUDY

- Acute retina necrosis is a rare disease, the study sample was small and follow up period was short. If the follow up period was extended more complications may be found.
- Sole oral antiviral therapy was started on patients with indolent acute retinal necrosis and combined therapy was started in more severe cases. This results in difference in both initial and final visual acuity.

SUMMARY

- Acute retinal necrosis had equal prevalence in both male and female
- Our study reveals a bi modal age group distribution with peak prevalence at 16-25 and 45-65 age group as reported in various litratures
- ARN is most common in immunocompetent patients than immunocompromised
- Most common pervious history of viral infection was chicken pox
- ARN has both anterior and posterior segment involvement
- Most common virus isolated from vitreous sample was Varicella zoster as reported in various literature
- Retinal detachment is the most common complication of ARN
- Prompt treatment is required to prevent retinal detachment and fellow eye involvement
- Primary treatment with oral antiviral for indolent ARN is an effective alternate to combined therapy as the later is invasive and requires hospitalization.
- This study proves treatment outcome is better in oral antiviral in comparison to combined therapy

CONCLUSION

Acute retinal necrosis is rare but potential blinding disease, polymerase chain reaction on ocular fluids helps to identify viral DNA and appropriate treatment can be instituted. Oral antiviral and intravitreal antiviral are increasingly used in treatment of ARN. Primary treatment with oral antiviral for indolent ARN is an effective alternate to combined therapy as the later is invasive and requires hospitalization. Prompt diagnosis and good therapeutic approach is a must for better visual recovery. Vision threatening complication like retinal detachment can be prevented with judicious monitoring of ARN patients and prompt treatment. Despite, advances in treatment and diagnostic modalities available like polymerase chain reaction (PCR) to identify virus with intraocular fluid, ARN continues to remain as an ophthalmological emergency with retinal lesion progressing rapidly after the disease onset. Precise understanding about this disease condition by ophthalmologist is at most important for prompt diagnosis and treatment.

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BIBLIOGRAPHY

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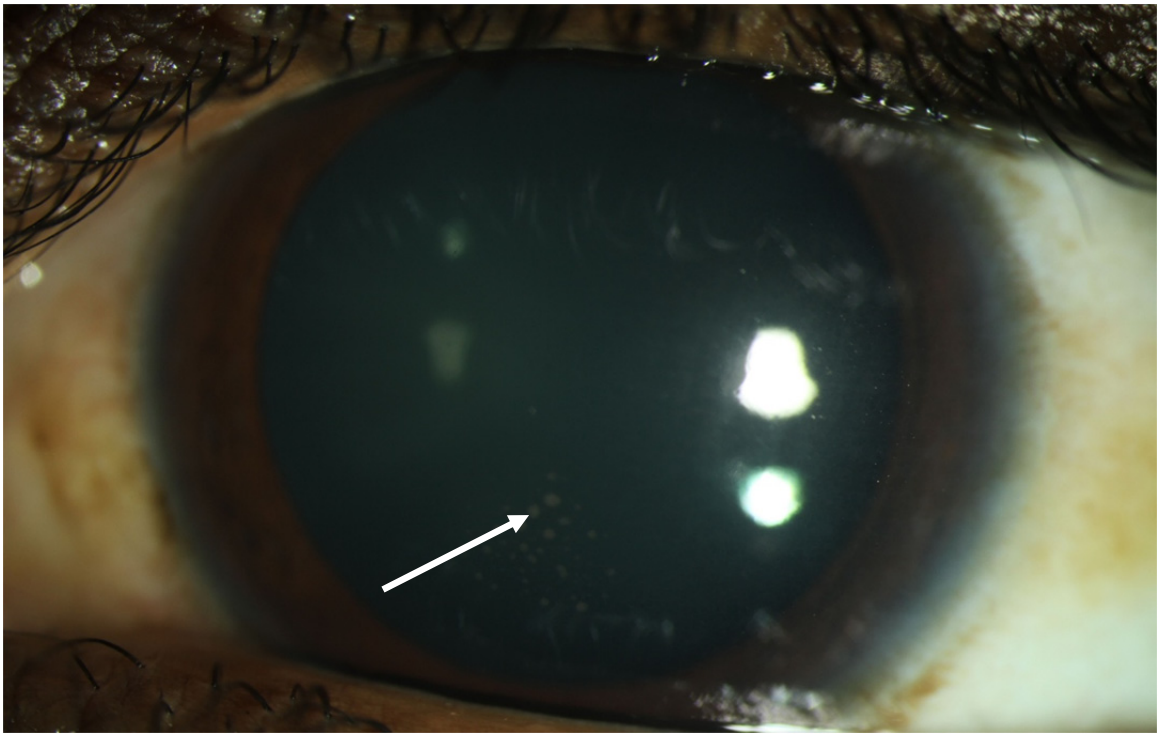
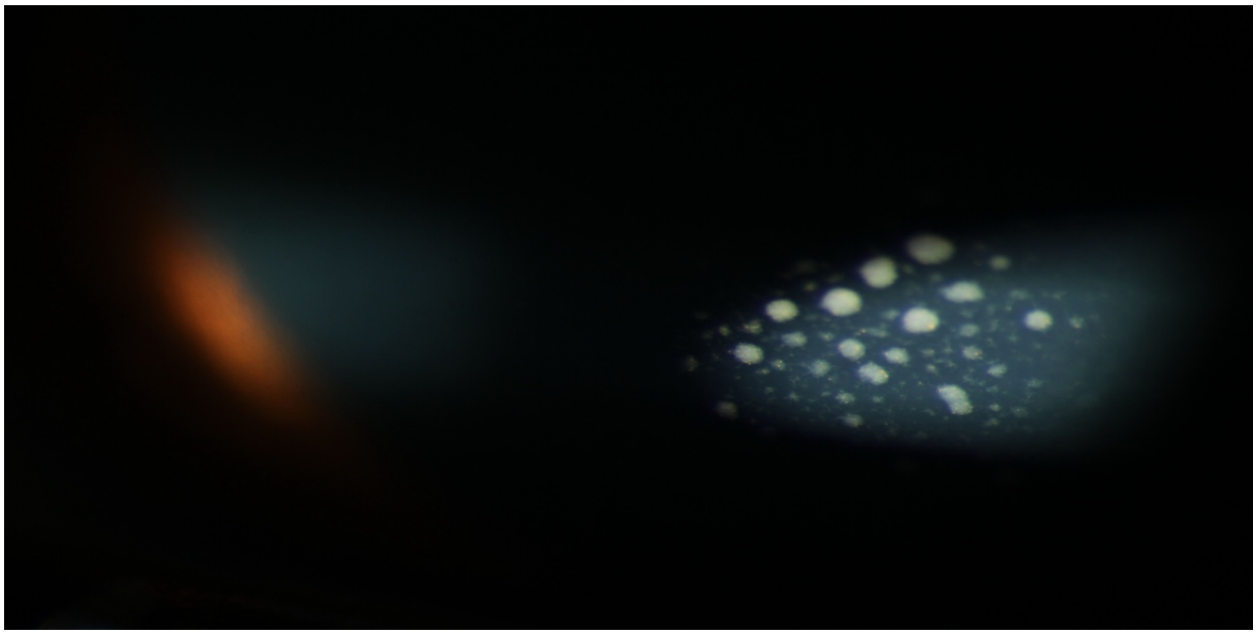
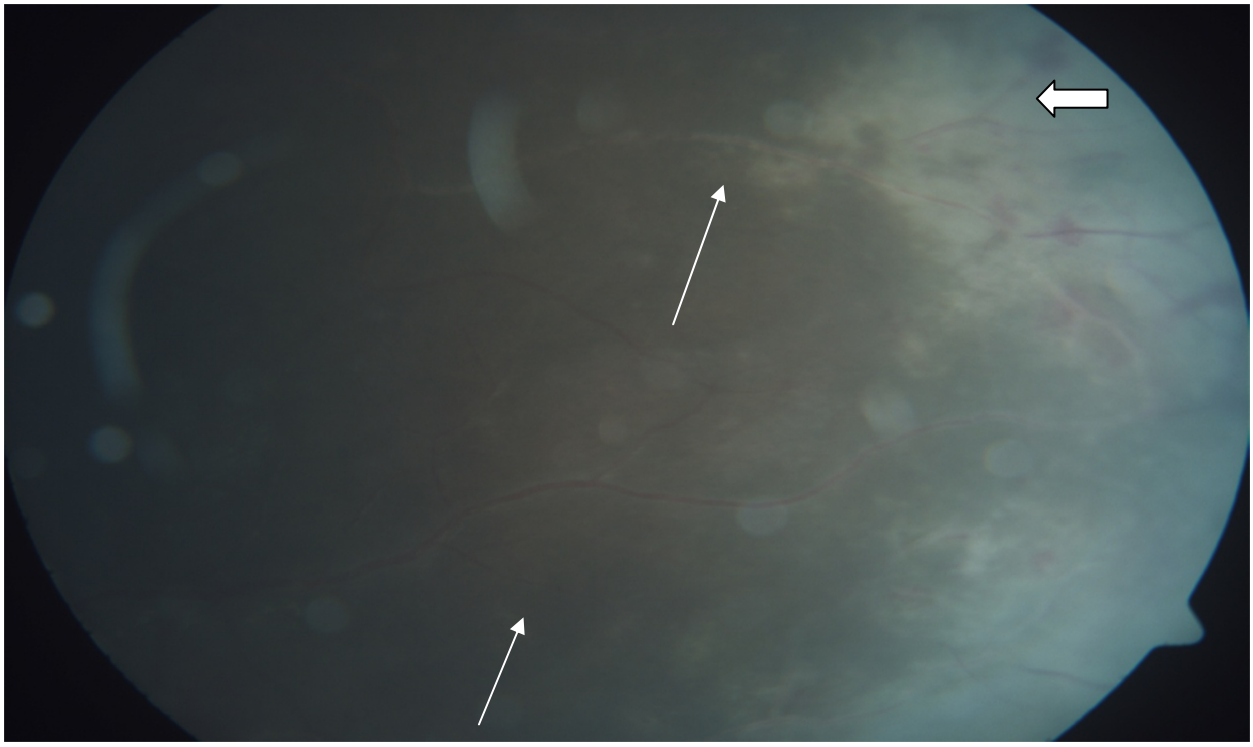
CLINICAL PICTURES



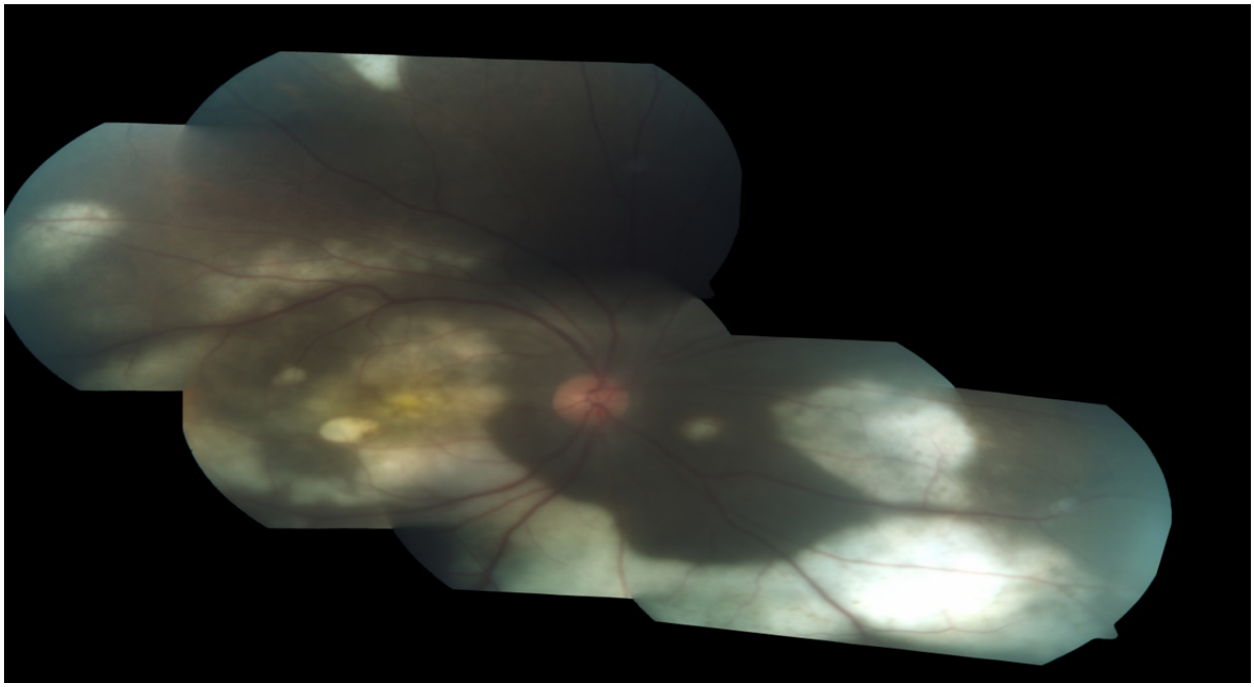
PICTURE 1: Arrow indicating fresh Granulomatous keratic precipitates in ARN patient



PICTURE 2: Magnified view of Granulomatous keratic precipitates with cells and flare in anterior chamber

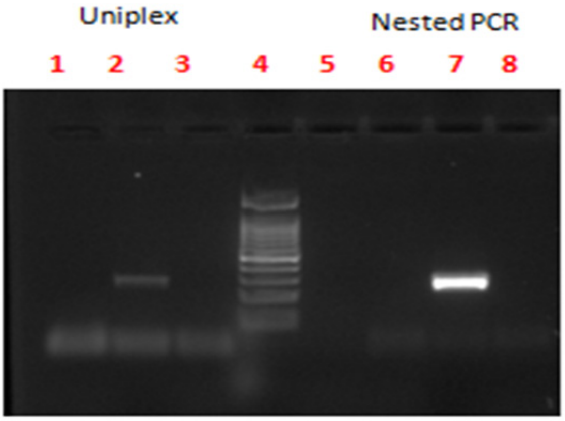


PICTURE 3: Fundus photo of ARN patient showing vitritis. (i) slender arrows indicating occlusive vasculitis (ii) broad arrow white patch of retinal necrosis at periphery of retina.



PICTURE 4: Fundus montage of ARN patient showing Retinal necrosis

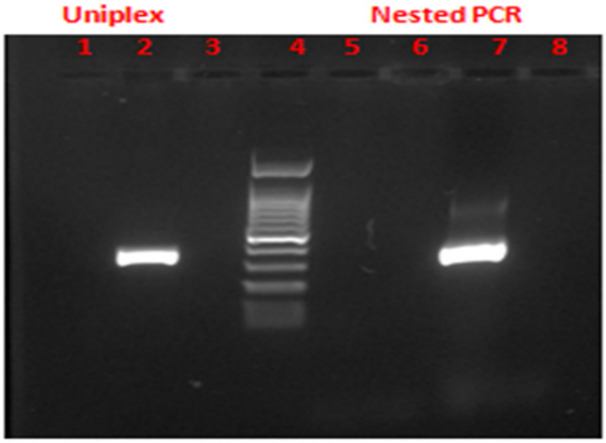
HSV



HSV Uniplex PCR:Lane 1: NC, Lane 2:PC, Lane 3:S1,Lane 4 :100bp DNA ladder, HSV NESTED PCR: Lane 5:NC,Lane 6:NC 1 Lane 7: PC, Lane 8: S1

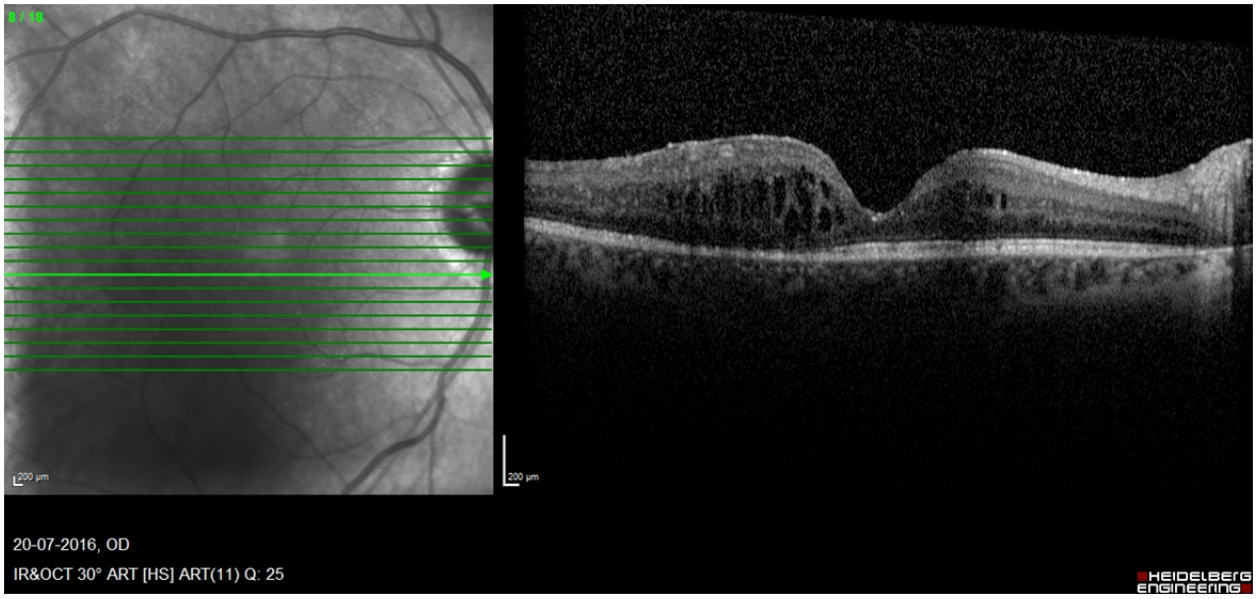
PICTURE 5: PCR for HSV DNA analysis. Lane 3&8 is patient same showing negativity for HSV. Lane 2&7 HSV positive

VZV



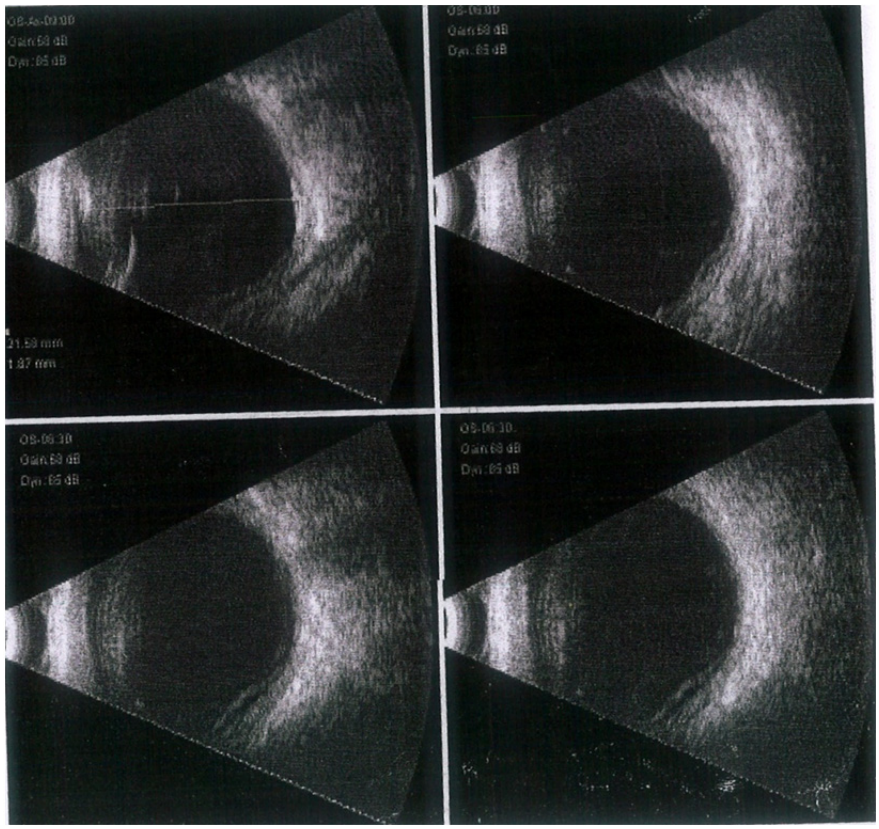
VZV Uniplex PCR:Lane 1: NC, Lane 2:PC, Lane 3:S1,Lane 4 :100bp DNA ladder, VZV NESTED PCR: Lane 5:NC,Lane 6:NC 1 Lane 7: PC, Lane 8: S1

PICTURE 6: PCR for VZV DNA analysis, lane3&8 shows negativity for VZV in patients sample. Lane 2&7 are positive control.



PICTURE 7: Spectral domain OCT in ARN patient showing macular edema.

PICTURE 8: USG B scan showing Inferior Retinal Detachment with vitritis



ANNEXURE

ABBREVIATION

- ARN : Acute retinal necrosis
- AIDS : Acquired immuno deficiency syndrome
- CMV : Cytomegalo virus
- FFA : Fundus fluorescein angiography
- HIV : Human immuno virus
- HSV : Herpes simplex virus
- LogMar : Logarithm of the minimum angle of resolution
- OCT : Optical coherence tomography
- PCR : Polymerase chain reaction
- USG-B scan: Ultra sonography B scan
- VZV : Varicella zoster

PROFORMA

1. Serial no :

2 .Date:

3. Name:

4. Age:

5. Sex:

6. Address:

7. Contact number:

8. MR number:

9. Eye affected:

RE	**LE**	**BOTH**

10. Occurrence of 2nd eye after 1st eye

yes	**no**

11. Time gap:

12. Same eye affected again

yes	**no**

13. Time gap:

14. Immune status

immunocompetent	**Immunocompromised**

HISTORY

1. h/o chicken pox (HSV infection)

yes	**no**

2. if yes, when:

3. h/o shingles (HZV infection):

yes	**no**

4. if yes, when:

5.

HISTORY	**RE**	**LE**
fever		
Head ache		
Neck stiffness		
Ocular pain		
Periorbital pain		
FB sensation		
Red eye		
Pain during eye movement		
photophobia		
floaters		
Decreased peripheral vision		
dyschromatopsia		

OCULAR EXAMINATION

	RE	LE
LID a.lid edema b. others		
CONJUNCTIVA a. cilliary congestion b. SCH others		
CORNEA a. Dentritic ulcer b. Stomal keratitis c. others		

	RE	LE
SCLERA a. episcleritis b. scleritis c. others		
ANT. CHAMBER a. ac cells b. fine KPs c. granulomatous KPs d. hypopyon e. post. Synechae f. others		
IRIS		

PUPIL a. Size and shape b. RL c. RAPD d. others	**RE**	**LE**
LENS		
VITREOUS a. vitreous cells b. vitreous fibrosis c. vitritis d. others		
RETINA a. retinal necrosis and site b. retinal vasculitis c. retinal phlebitis d. retinal hemorrhages e. retinal holes f. retinal detachment g. others	**RE**	**LE**
OPTIC DISC a. disc edema b. pale disc c. hyperemic disc d. intraneural vasculitis e. loculated exudates f. others	**RE**	**LE**
MACULA		

IOP a. NCT b. applanation		

INVESTIGATION

1. Diagnostic vitrectomy done

yes	**no**

2. Specimen sent to PCR

yes	**no**

3. PCR result

HZV	**HSV**	**EBV**	**OTHERS**

TREATMENT

1. Oral treatment

DRUGS	DOSAGE	DURATION
acyclovir		
valacyclovir		
corticosteroids		
aspirin		
others		

2. Intra venous therapy

DRUGS	DOSAGE	DURATION
acyclovir		
others		

3. Intravitreal therapy

DRUGS	DOSAGE	DURATION
gancyclovir		
others		

VISUAL OUTCOME

TIME	SNELLENS	LogMAR
At presentation		
1st review		
2nd review		
3ed review		
4th review		
5th review		
6th review		
Final V/A		

RETINAL DETACHMENT OCCURENCE

EYE INVOLVED	TIME SINCE DIAGNOSIS
RE	
LE	
BOTH	

TREATMENT FOR RETINAL DETACHMENT

Treatment given	Yes	No
PPV		
Sclera buckle		
Endo laser		
Silicon oil tamponade		

SILICON OIL REMOVAL

YES	NO

If YES when:

Occurrence of RE-RD after silicon oil removal

Yes	No

CONSENT FORM

Informed Consent form to participate in a clinical trial

Study Title- Demography , Clinical Features, Etiology, Management And Outcomes in ACUTE RETINAL NECROSIS: A Prospective study

Protocol Number:

-

Subject's Name: _____Subject's Initials: _____

-

- Subject ID No: _____
- Date of Birth / Age: _____

		Please put initial in the box (Subject)
(i)	I confirm that I have understood the information about the study, procedures and treatments for the above study and have had the opportunity to ask questions and I received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. However, this is may not be possible for certain surgical procedures	[ ]
(iii)	I understand that the Investigator of the study to access my health records for the research purpose. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]

(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
(v)	I agree to take part in the above study	[ ]

Signature (or Thumb impression) of the Subject:

_____

Date: _____/_____/_____

Subject's Name:

_____

Signature (or Thumb impression) of Legally Acceptable Representative (LAR):

_____ Date: _____

Signature of the Investigator: _____Date:
_____/_____/_____

Investigator's Name:

_____

Signature of the Witness _____
Date:_____/_____/_____

Name of the Witness:

_____

Urkund Analysis Result

Analysed Document: THESIS ORIGINAL.docx (D30968420)
Submitted: 10/3/2017 7:11:00 AM
Submitted By: drkk81@gmail.com
Significance: 3 %

Sources included in the report:

http://eyewiki.aao.org/Acute_retinal_necrosis
https://link.springer.com/article/10.1007/s10792-009-9301-3
http://www.retina-specialist.com/article/a-novel-approach-for-rd-in-viral-retinitis
https://ohsu.pure.elsevier.com/en/publications/combination-systemic-and-intravitreal-antiviral-therapy-in-the-ma-4

Instances where selected sources appear:

16

SNO	NAME	AGE	GENDER	IMMUNE STATUS	EYE	VIRAL INFECTION	FEVER	HEADACHE	PHOTOPHOBIA	EYE PAIN	RED EYE	FLOATERS	DEFECTIVIE VISION	CONGESTION	KPS
1	TAMILARASAN	29	1	1	1	2	2	2	2	1	1	2	1	1	1
2	SUMATHI	19	2	1	1	2	2	2	2	1	1	2	1	1	1
3	ROOPAVATHY	50	2	1	1	1	2	2	1	1	2	1	1	2	1
4	NAGALINGAMMA	60	2	1	2	2	2	2	2	2	2	2	1	1	1
5	BASKAR	45	1	2	2	2	2	2	2	2	2	2	1	2	1
6	RAVI	47	1	2	1	2	2	2	2	2	1	2	1	1	1
7	THANGAMANI	43	2	1	2	2	2	2	2	2	1	2	1	1	1
8	VIJAYAKUMAR	32	1	1	2	1	2	2	2	1	1	2	1	1	1
9	RAJAMANI	65	1	2	1	2	2	2	2	1	1	2	1	1	1
10	HAKKIM	43	1	1	1	1	1	1	1	2	1	1	1	1	1
11					2				1	2	1	1	1	1	1
12	PACKEER MOHAMMED	65	1	1	1	2	2	2	2	2	1	1	1	1	1
13	MANI	57	2	1	2	2	2	2	2	2	1	2	1	1	1
14	RAJENDERAN	59	1	2	1	2	2	2	1	1	1	2	1	1	1
15	LAKSHMI	62	2	1	2	2	2	2	2	2	1	2	1	1	1
16	ANANDHAVALLI	28	2	1	2	1	2	2	1	1	1	2	1	1	1
17	LATHA	26	2	1	1	2	2	2	1	2	1	1	1	1	1
18	VANITHA	32	2	1	2	2	2	2	2	1	1	2	1	1	1
19	MURUGAIAH	54	1	1	1	2	2	2	2	1	2	1	1	1	1
20	JOTHIMANI	46	2	1	1	2	2	2	2	1	1	1	1	1	1
21	SHANMUGAPANDI	21	1	1	2	2	2	2	1	2	1	1	1	2	1
22	SRINIVASAROA	43	1	1	1	2	2	2	2	2	1	2	1	1	1
23	MALAKONDAIAH	36	1	1	1	2	2	2	2	1	1	2	1	1	1
24	PANDI	39	1	1	1	2	2	2	1	1	1	1	1	1	1
25	VENKATASUBBA ROA	42	1	1	2	1	2	2	1	1	1	2	1	1	1
26	SURESH	34	1	2	2	2	2	2	1	1	1	1	1	1	1
27	ARUNA	29	2	1	1	2	2	2	2	1	1	2	1	1	1
28					2	2				1	1	2	1	1	1
29	JAYALAKSHMI	49	2	1	2	2	2	2	2	1	1	2	1	1	1
30	AJITHKUMAR	18	1	1	1	1	2	2	1	1	1	1	1	1	1
31	KARUNANITHI	48	1	1	2	2	2	2	1	1	1	2	1	1	1

CELLS	FLARE	POST SYNECHAE	VITRITIS	VASCULITIS	COMPICATED CATARACT	RETINAL NECROSIS	CLOCK HOUR OF ARN	PCR	PCR RESULTS	TREATMENT	INTIAL VISION	FINAL VISION	OCCURANCE OF RD
1	1	2	1	1	1	1	4	1	3	2	4\60	1\60	1
1	1	2	1	1	2	1	8	1	3	2	6\18	6\24	1
1	1	2	1	1	1	1	2	2		1	6\18	6\18	2
1	1	1	1	1	1	1	3	1	3	2	PL	FCF	2
1	1	2	1	1	2	1	3	2		1	5\60	6\36	2
1	1	2	1	1	2	1	10	1		2	1\60		
1	1	2	1	1	2	1	3	1	2	2	6\24	6\18	2
1	1	2	1	1	2	1	6	1	3	2	PL	HM	1
1	1	2	1	1	2	1	4	2		1	6\36	6\18	2
1	1	2	1	1	2	1	4	2		1	6\9	6\6	2
1	1	2	1	1	2	1	6	2		1	6\36	6\24	2
1	1	2	1	1	1	1	6	2		2	6\60	6\9	2
1	1	2	1	1	2	1	4	2		1	5\60	6\12	2
1	1	2	1	1	2	1	4	2		1	5\60	6\60	1
1	1	2	1	1	1	1	6	2		1	6\36		
1	1	2	1	1	2	1	6	2		1	6\36	6\9	2
1	1	2	1	1	2	1	3	1	3	2	6\18	6\12	2
1	1	1	1	1	1	1	3	1		1	6\60	6\18	2
1	1	2	1	1	2	1	3	2		1	6\12	6\18	2
1	1	2	1	1	2	1	6	2		1	6\12	6\12	2
1	1	2	1	1	2	1	12	2		1	6\9	6\9	2
1	1	1	1	1	2	1	2	2		1	6\36	6\24	2
1	1	2	1	1	2	1	5	2		2	6\24	6\12	1
1	1	2	1	1	2	1	7	2		2	6\24	6\60	1
1	1	1	1	1	2	1	3	2		1	6\12	6\18	2
1	1	2	1	1	2	1	4	2		2	6\60	6\36	1
1	1	2	1	1	2	1	3	2		1	6\60	6\36	2
1	1	2	1	1	2	1	3	2		1	HM	6\9	2
1	1	2	1	1	2	1	12	1	3	2	6\60	6\36	1
1	1	2	1	1	2	1	8	1	2	2	6\36	6\36	1
1	1	2	1	1	1	1	6	1	3	2	6\60	6\60	1

TIME GAP OF OCCURANCE RD	PPV	SOI	SOR	WHEN SOR DONE	RE RD AFTER SOR	VISION BEFORE RD SX	VISION AFTER RD SX	SEC GLAUCOMA	FELLOW EYE INVOLVEMENT	TIME GAP FELLOW INVOLVEMENT
0	1	1	2			1\60	1\60	2	2	
1	1	1	1	2	2	6\18	6\24	2	2	
								2	2	
								2	2	
								2	2	
								2	2	
5	1	1	1	4	1	PL	HM	2	2	
								2	2	
								2	2	
								2	1	3
								2	2	
								2	2	
14	1	1	2			PL	6\60	2	2	
								2	2	
								2	2	
								1	2	
								2	2	
								1	2	
								2	2	
								2	2	
6	1	1	1	3	2	6\60	6\12	2	2	
6	1	1	1	3	2	3\60	6\60	2	2	
								1	2	
0	1	1	2					2	2	
								1	2	
0	1	1	2					2	2	
								2	2	
								2	2	2
8	1	1	1	4	2	6\60	6\36	2	2	
0	1	1	1	4	1	6\36	6\36	2	2	
2	1	1	1	3	2	6\60	6\60	2	2	

SNO	NAME	AGE	GENDER	IMMUNE STATUS	EYE	VIRAL INFECTION	FEVER	HEADACHE	PHOTOPHOBIA	EYE PAIN	RED EYE	FLOATERS	DEFECTIVIE VISION	CONGESTION	KPS
		in years	MALE=1	IMMUNOCOMPETENT=1	RE=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1
			FEMALE=2	IMMUNOCOMPROMISED=2	LE=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2

CELLS	FLARE	POST SYNECHAE	VITRITIS	VASCULITIS	COMPICATED CATARACT	RETINAL NECROSIS	CLOCK HOUR OF ARN	PCR	PCR RESULTS	TREATMENT	INTIAL VISION
YES=1	YES=1	YES=1	YES=1	YES=1	YES=1	YES=1		DONE=1	HSV=1	ORAL THERAPY=1	in snellens,conerted to LogMar
NO=2	NO=2	NO=2	NO=2	NO=2	NO=2	NO=2		NOT DONE=2	VZV=2	COMBINED THERAPY=2	
									NO ORGANISM=3		

FINAL VISION	OCCURANCE OF RD	TIME GAP OF OCCURANCE RD	PPV	SOI	SOR	WHEN SOR DONE	RE RD AFTER SOR	VISION BEFORE RD SX
in snellens,conerted to LogMar	YES=1	in weeks	YES=1	YES=1	YES=1	in months	YES=1	in snellens,conerted to LogMar
	NO=2		NO=2	NO=2	NO=2		NO=2	

VISION AFTER RD SX	SEC GLAUCOMA	FELLOW EYE INVOLVEMENT	TIME GAP FELLOW INVOLVEMENT
in snellens,conerted to LogMar	YES=1	YES=1	in weeks
	NO=2	NO=2	